The Oxford Medicine

BY VARIOUS AUTHORS

VOLUME V

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By DAVID JOHN DAVIS

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Septic sore throat is an acute primary infection of the pharynx and/or the tonsils characterized by a sudden onset severe sore throat fever and marked prostration It occurs usually as an epidemic Its cause is a hemolytic streptococcus The symptoms course bacteriology epidemiology and pathology constitute a definite clinical entity as a rule readily identifiable A possible relation of the disease to the milk supply should be investigated at once Such a connection may or may not exist or be readily apparent Contact and aerial transmission of the disease also occurs

In the medical literature of different countries and at different times septic sore throat has had a varied nomenclature The following terms may be considered synonymous or approximately so streptococcal sore *throat acute pharyngitis erysipelas of the throat pseudo membranous*

CHAPTER I

SEPTIC SORE THROAT

By DAVID JOHN DAVIS

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Introduction

Septic sore throat is an acute primary infection of the pharynx and/or the tonsils characterized by a sudden onset, severe sore throat, fever and marked prostration. It occurs usually as an epidemic. Its cause is a hemolytic streptococcus. The symptoms, course, bacteriology, epidemiology and pathology constitute a definite clinical entity, as a rule readily identifiable. A possible relation of the disease to the milk supply should be investigated at once. Such a connection may or may not exist or be readily apparent. Contact and aerial transmission of the disease also occurs.

In the medical literature of different countries and at different times septic sore throat has had a varied nomenclature. The following terms may be considered synonymous or approximately so: streptococcal sore throat, acute pharyngitis, erysipelas of the throat, pseudo membranous

may be enlarged and very red The clinical picture may resemble influenza A pharyngeal culture will yield hemolytic streptococci in large numbers

EPIDEMIOLOGY

In England for many years septic sore throat was recognized as a not infrequent epidemic infection often bearing an etiological relation to the milk supply Long ago Savage[1] collected data on 18 different outbreaks that occured between 1860 and 1905 In Christiania Norway in 1908 a serious epidemic of 548 cases broke out, the source of which was traced definitely to a cow suffering with mastitis

In the United States the first epidemic of sore throat recognized as having a definite relation to the milk supply appeared in Boston in 1911 with an estimated total of 1 400 cases Later the following serious outbreaks occurred Chicago[3,4] in 1912 with an estimated 10 000 cases Baltimore [6] in 1912 with 1 000 cases Wakefield and Stoneham Mass with 1 000 cases[9] Concord New Hampshire[7] Cortland and Homer New York[8] 669 cases, Rockville Center New York[10] Jacksonville Ill 348 cases[11] Galesville 325 cases[1] Baraboo Wis 74 cases Portland Oregon 487 cases

Many smaller epidemics have appeared from time to time in towns especially in the eastern part of the United States[14] In England too many small outbreaks occurred involving as a rule from a few score to several hundred persons No doubt there have been many epidemics in this and other countries but because of the similarity to ordinary outbreaks of colds and pharyngitis their origin and relation to the milk supply were not recognized

As shown by the studies of Capps Davis Winslow Frost and others the striking epidemiological feature has been the relation between the outbreaks and a single milk supply The epidemics are invariably explosive in character the maximum number of cases appearing usually in the course of a few days This maximum lasting from one to several days recedes rapidly at first then somewhat more gradually than it arose and for some little time thereafter a few cases continue to appear As a rule the epidemics last from to 4 weeks In certain outbreaks (Boston Chicago and Baltimore) a few days in advance of the main epidemic a sharp rise in the number of cases lasting a day or more occurred

An interesting feature in most of the epidemics was the small percentage of contact cases that appeared In general 60 70 and 80 per

sore throat phlegmonous tonsilitis cynanche angina maligna and putrid sore throat

Symptoms and Course

Of importance is the fact that outbreaks of septic sore throat are as a rule observed first by the general physician Only later is the outbreak reported to health officers and consultants The doctor s attention is first arrested by the sudden appearance in a relatively limited locality of a number of patients with complaints and symptoms as follows

The onset usually is sudden accompanied by chills or rigor pain in swallowing general muscular soreness a dull severe headache and in some instances, by nausea and vomiting The temperature rises to 102 to 105° F, and during the first 2 or 3 days prostration often is extreme The throat is variable in appearance Early there is diffuse redness of tonsils and pharynx which in a few hours becomes more intense and general Often isolated patches of gray exudate limited to the mouths of the crypts appear Not infrequently an extensive membranous exudate resembling diphtheria spreads over the tonsils or throat On pressure the tonsils are tender and from the crypts pus exudes rich in streptococci and leucocytes

The pulse often is slow there being not only a relative but an absolute bradycardia At times a pulse of 40 or lower is found in patients with fever of 102 F or more In some epidemics this slow pulse has not been noted The blood picture is that of a severe pyogenic infection without noteworthy peculiarities Leucocytosis usually occurs and in complicated cases may be extremely high In 2 such patients the writer observed counts of over 60 000 Differential counts reveal a polynucleosis

In the milder cases in 2 to 4 days the fever subsides leaving the patient weak and easily fatigued for several days longer The average period of illness in 200 cases recorded by Capps was between 9 and 10 days but often late within this period the patient may experience a relapse manifested by a remittent or intermittent type of fever and other signs pointing to a local infection or perhaps to pyemia or septicemia This stage of the disease may present a variable clinical picture and the course and outcome may be determined by the nature of possible complications

Pilot[10] has called attention to a possible variation of the symptoms in patients whose tonsils have been removed Sore throat may be largely absent but the follicles of the pharynx and at the base of the tongue

As a rule in afflicted households the family incidence has been heavy Women are infected more frequently than men In Christiania Boston and Galesville adults were stricken more often than children In Baltimore adults and children were affected about equally

It is to be noted that all epidemics of streptococcus sore throat are not milk borne A complete analysis of outbreaks in army camps in which no relation to milk supply could be found has been made by Bloomfield and Rantz[31] As many as 10 per cent of 3 000 men in one unit developed a streptococcal sore throat very similar to the septic sore throat of milk borne epidemics Such outbreaks have not been considered as belonging in the group of septic sore throat of milk origin Their epidemiology differs in certain respects being less explosive and the symptoms on the whole being less malignant

Bacteriology

Hemolytic streptococci are unquestionably the specific cause in all epidemics being found in abundance early in the tonsils and throats and in many fluids and secretions of the infected persons The properties of the streptococci found in the various epidemics while varying slightly in certain details agree in their more important characteristics These minor variations even though slight may be important in tracing out sources of infection in epidemics (Theobald Smith) According to Holman s classification the strains fall in the streptococcus pyogenes group In Schottmuller s classification they belong to the streptococcus hemolyticus type Smith and Brown[14] called them the beta type of the streptococcus hemolyticus Davis as a descriptive term used streptococcus epidemicus Lancefield places them in her large group A of hemolytic streptococci In a recent analysis of group A Alice Evans[3] in an intensive study of the fermentative agglutinative and immunological behavior of many strains reveals certain correlations pointing to several species including among others streptococcus scarlatinae streptococcus pyogenes and streptococcus epidemicus Further studies she states are required for a final analysis

The streptococci grow freely on ascites blood agar often as large watery mucoid colonies They are usually definitely encapsulated They do not hydrolyze sodium hippurate nor do they ferment mannite

cent or more of all persons stricken were those consuming the suspicious milk. Winslow states that the disease in Boston was almost non contagious, the curve being so compact as to almost preclude the occurrence of any large number of secondary cases derived by contact from the primary outbreak. Capps[3] records an instance where the nurses in two Chicago hospitals although occupying the same dormitory received two different milk supplies, one being from the suspected dairy. The nurses using this milk were heavily infected (50 per cent), the other group, although coming in intimate contact with them, escaped entirely.

To the above statements relative to the infrequency of contacts there are apparently a few exceptions. Sore throat spread in prosodemic fashion in adjacent towns preceding the Boston outbreak; in Baltimore a prosodemic outbreak followed the milk epidemic. Winslow and Hubbard[1] report an outbreak of 905 cases in Westchester County, New York, the evidence indicating that the infection was spread mainly by contact. There is abundant evidence that ordinary streptococcus tonsillitis is transmitted commonly by direct contact, and one would expect that the highly virulent milk infections might be even more easily transmitted in this manner. In general, however, this does not seem to be the case.

The outbreaks have occurred with striking regularity in the winter and spring months and practically all are included from October to May.

Years ago they appeared both in large and small cities. At present they are appearing only in small towns where pasteurization still is absent or imperfect. In recent years no epidemics have occurred in large cities.

In the United States during the 10 years 1936-1945 the U. S. Public Health Service summarizes the number of milk borne epidemics of both sore throat and scarlet fever as follows:

Year	*Outbreaks*	*Cases*
1936	18	1,553
1937	14	1,384
1938	1[illegible]	674
1939	9	1,324
1940	5	482
1941	3	[illegible]19
194[illegible]	6	620
1943	4	233
1944	2	171
1945	3	237

Pathology

In most cases the tonsils are affected primarily and chiefly In fatal cases dying early they are swollen and red and the crypts are filled with grayish tenacious fibrinopurulent exudate containing many strepto cocci Microscopically they may reveal necrosis of the follicles and extensive septic thrombi in the blood vessels The regional cervical lymph nodes are hyperplastic and may break down with purulent discharge They may become so large as to simulate Hodgkin's disease Death results from serious complications among which the most important are peritonitis otitis media meningitis pneumonia empyema septicemia, endocarditis and erysipelas In general the morbid anatomy is that revealed by these various conditions when caused by a highly acute and virulent streptococcus infection The exudates in the various cavities are serofibrinous later becoming purulent with intense congestion and edema of the serous and adjacent tissues

Period of Incubation

The period of incubation appears to be 2 to 4 days Capps reported individuals known to be directly exposed to the cough of infected per sons becoming ill in 30 hours Henika and Thompson[13] state that when ever the incubation period was 3 to 4 days the case was mild The severer cases came down within 48 hours after exposure In the Chicago milk borne epidemic the incidence curve in relation to the failure to pasteurize rose promptly in the following 2 to 4 days Epidemics have been known to stop promptly within 48 hours after instituting pasteur-ization

Complications

A serious feature of septic sore throat is the common occurrence of many dangerous complications The streptococci are prone to spread from the throat in three ways (1) along mucous membranes to adjacent channels cavities sinuses or surfaces (2) through lymphatics to regional structures especially lymph nodes (3) by the blood stream to distant parts of the body

1 Otitis media is not an uncommon complication although it occurs perhaps less often than one would expect Hemolytic streptococci are found in the pus Acute meningitis may follow from extension of the

Transmission

Two sources of streptococci causing milk borne epidemics of sore throat are recognized the one human some lesion in throats hands etc of milkers or handlers the other bovine the udder or teats of the cow On account of the similarity of streptococci found in diseased udders and those found in human throats it may be difficult to prove in a given case whether the infection is bovine or human in origin The ultimate sources no doubt are variable and at times indeterminable For example in 1935 in the U S there were 9 outbreaks of sore throat with sources as follows so far as could be determined, human carriers -, infected finger 2, infected cow patients , infected milk 1

One can readily understand how a human streptococcus carrier may contaminate a milk supply through sore throat contaminated hands and the like No doubt at times this method of transmission occurs but many facts are now available indicating that the source is the udder of the milch cow, where the streptococci may grow in large numbers for a long period of time Among these facts are the explosive and sustained nature of certain epidemics indicating massive dosage the subsidence of epidemics after the removal of the suspected cow often failure to locate a human carrier the presence of hemolytic streptococci in the suspected milk from cows suffering with mastitis which streptococci have been identified morphologically, culturally and immunologically with those from the human cases

It has been shown experimentally that bacteria may readily enter the udder from the outside through the meatus of the teat Davis and Capps[1] years ago proved that streptococci smeared on the outer surface of the teat would readily cause an enduring mastitis especially if a small abrasion was made about the meatus This observation was confirmed and extended later by Mathers , Savage[1] and others

While milk raw or imperfectly pasteurized is the vehicle of most of these milk borne epidemics in certain instances milk products have played a role in the transmission Cream ice cream and butter all have been implicated These products are frequently made from unpasteurized milk In this connection a unique method of transmission of sore throat was described by Allen and Baer[3] The machine the mechanical cow , used in the reconstitution of powdered milk was contaminated by a streptococcus carrier resulting in an explosive epidemic of sore throat

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process, but this is rare, or the meningitis may result directly from the septicemia A number of observers have noted conjunctivitis Infection of the various nasal sinuses is seen occasionally Acute pharyngitis with marked hoarseness is not uncommon Bronchitis is a common complication often going on to bronchopneumonia Pleurisy may develop Empyema occurs not infrequently Glossitis and stomatitis are noted rarely Enteritis and diarrhea are not common

2 Neighboring structures frequently become infected through lymph channels Peritonsillar abscess and suppuration of cervical lymph nodes appear often In many cases the enlarged lymph nodes at the angle of the jaw are characteristic The spleen often is palpable Erysipelas occurs usually about the neck or face and is serious

3 Direct invasion of the blood stream commonly occurs I have observed infected thrombi in the blood vessels of the tonsils and regional tissues post mortem Blood cultures usually are negative early and in mild cases but in the more severe cases and in those presenting signs of serious complications streptococci may be cultivated from the peripheral blood Septicemia often is rapidly fatal and usually is accompanied by some other more or less definitely localized infection of which the most common are peritonitis arthritis endocarditis and pericarditis Peritonitis is the most frequent cause of death It comes on with pain and may be mistaken for appendicitis for which operations have been performed Seen early the peritoneum is hyperemic and contains a turbid serous or serofibrinous fluid with leukocytes and streptococci Death follows rapidly Arthritis manifests itself as a mild or severe multiple joint infection frequently of the extremities The symptoms subside in a few days and rarely go on to suppuration Endocarditis may or may not be associated with the arthritis It may be a simple vegetative lesion or a more serious and extensive involvement of the valves Pericarditis has been observed but apparently is not very common

Rheumatic fever is occupying a more and more important place in the category of all post-streptococcic manifestations and sequelae Griffith[33] from a study of a large group of military cases concludes that rheumatic fever definitely follows about 5 per cent of cases of all streptococcus throat infections and that it is logical therefore to consider every patient with a throat infection due to hemolytic streptococci as a potential rheumatic subject As a preventive measure he suggests the early institution of proper salicylate therapy Penicillin and sulfonamide drugs are not indicated and may do harm in rheumatic fever

Albuminuria and nephritis the latter sometimes hemorrhagic in character occur and are probably a result of the severe toxemia rather than a definite renal infection The termination usually is favorable

A great variety of skin lesions have been described of which the most important are rashes variable in appearance some simulating scarlet fever Others resemble erysipelas and a few are definitely purpuric These skin rashes have been observed in varying proportions of cases in different outbreaks At times they are evanescent and indefinite In other outbreaks they closely simulate or are identical with scarlet fever This has led to confusion in diagnosis Certain observers especially in England have the belief supported by some striking evidence that the causal streptococci of sore throat and scarlet fever are virtually identical, but that they vary only in their ability to call forth specific skin reactions in the host this difference having been caused by an earlier infection with a rash producing strain of streptococci

Diagnosis

The explosive nature of the outbreak and the restriction to a localized region or institution especially if there is a common milk supply are important points in determining the existence of an epidemic and should be considered by all physicians and health officers There is little doubt that many milk borne epidemics of sore throat have not been recognized on account of failure to note the above points It may be difficult or impossible to diagnose the individual case in an epidemic from the severe sporadic cases of streptococcus sore throat that occur commonly but taken as a whole the former are more severe present greater prostration and are more prone to serious complications

Individual cases may be confused with a variety of other conditions The profuse grayish membrane simulates diphtheria and during these epidemics the throat swabs sent to diagnostic laboratories for diphtheria examination increase strikingly Smears and cultures properly made on blood agar will differentiate The marked adenitis has been mistaken for mumps and even may suggest Hodgkin s disease Certain cases with rashes are difficult to differentiate from scarlet fever a history of exposure will aid The arthritis that appears may resemble or be followed by acute rheumatic fever Erysipelas appears to be identical etiologically and clinically with that originating under other conditions Pains in the abdomen vomiting and other signs suggesting peritoneal involvement

process, but this is rare or the meningitis may result directly from the septicemia A number of observers have noted conjunctivitis Infection of the various nasal sinuses is seen occasionally Acute pharyngitis with marked hoarseness is not uncommon Bronchitis is a common complication often going on to bronchopneumonia Pleurisy may develop Empyema occurs not infrequently Glossitis and stomatitis are noted rarely Enteritis and diarrhea are not common

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of thrombophlebitis adenitis and bronchopneumonia that may exist, 30 000 every 3 hours is sufficient to control all Group A hemolytic streptococci that may vary in their penicillin sensitivity (Pilot)

In the home the milder cases may be treated by intramuscular injections of the Romansky formula of 300,000 units in beeswax once or twice a day Sulfadiazine given in 1 gram doses every 4 hours will control the mild and moderately severe cases, when penicillin is not available During the administration of sulfa drugs the leucocyte count should be watched If no marked improvement occurs in 48 hours the streptococcus strain may be sulfa resistant as was discovered in certain epidemics in army camps Streptococcus anti serums are no longer necessary

The local use of penicillin preparations in septic sore throat in the form of lozenges gargles, sprays mouth washes or local applications has been recommended Such local action however on throat lesions is limited and should only supplement not replace the intramuscular use of penicillin preparations In times of high incidence or epidemic spread of sore throat the daily administration of ½ to 1 gram of sulfadiazine will reduce the number of cases Again sulfa resistant strains should be watched for their appearance

The use of penicillin and sulfadiazine has been an effective means of reducing the frequency of complications such as otitis media and adenitis Surgical intervention for peritonsillar abscess cervical abscess otitis media and mastitis seldom are necessary as compared with our experience of a few years ago

Rheumatic complications and glomerular nephritis may occur and are not prevented or profoundly influenced by the antibiotic or sulfa drugs

Prevention

The several modes of transmission of the disease permit effective preventive measures Thorough pasteurization under proper inspection is necessary to insure a safe milk supply Accidents in plant making it necessary temporarily to discontinue pasteurization should be made known to the consumers and to the health officers No doubt some of the pasteurization and inspection of milk as conducted at present is still inadequate although greatly improved in recent years

The causal streptococci are killed in milk by heating to the accepted pasteurization standards Consequently efficient pasteurization furnishes

always are alarming since general peritonitis is so common and so often fatal Acute appendicitis is to be kept in mind

Prognosis

In general milk borne septic sore throat is not the serious disease it was a generation ago Many epidemics reported in recent years reveal no deaths (U S P H Reports) The mortality ranges from 0 to 3 per cent In the list of milk borne septic sore throat and scarlet fever epidemics reported from 1923 to 1941 inclusive by the U S P H Service there were 17 891 cases and 18? deaths giving an overall mortality rate of 1 02 per cent Death is caused usually by one or more of the serious complications already mentioned

Treatment

Rigid quarantine should be instituted

On account of the severe toxemia patients should have rest in bed and should not be permitted to get up until the throat symptoms have cleared and the period of complications has passed Moderate catharsis is indicated Adequate intake of fluids and nourishment should be carefully supervised since on account of the pain in swallowing patients especially children may not receive an amount sufficient for their needs The temperature may be controlled by sponging and an ice pack applied to the neck gives comfort An antiseptic alkaline mouth wash should be used several times a day it may also be used as a gargle The teeth should be kept clean The value of sprays is doubtful Violent local applications or manipulation should be avoided, since the throat is tender and the infection might be disseminated in this way Aspirin has been commonly used for the temporary relief of pain

Peritonsillar abscess requires proper surgical treatment Cervical buboes usually resolve even though very large They should be incised only when fluctuation is evident

As in many other infections the treatment of septic sore throat recently has undergone radical changes The remedy of choice at present is penicillin Severe cases should receive an initial large dose 60 000 units or more intramuscularly and 60 000 units every 3 hours in order to establish a blood level sufficient to control the severe complications

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complete protection In other words universal pasteurization will practically eradicate these milk borne streptococcal epidemics

As to the use of raw milk the Boston epidemic, although occurring a generation ago still furnishes our most instructive lesson The Deerfoot Dairy was a model dairy in every respect with all possible safeguards taken to exclude disease in the cows and among the milkers and handlers through systematic laboratory examinations made under the direction of a competent bacteriologist and sanitarian Winslow stated in his report If in spite of such precautions the Deerfoot milk became infected any raw milk may at any time become infected There is but one certain safeguard against such outbreaks, proper pasteurization" However careful and rigid the examination may be, it is practically impossible surely and constantly to exclude mild and unrecognized cases of streptococcal infections either in man or in the cow

Probably in all epidemics a small but variable proportion of cases arise *from contacts and this mode of transmission should be controlled* To do this sore throat should be made a reportable disease as soon as there is indication of its becoming epidemic and proper quarantine regulations should be enforced at once Very little is known about immunity or resistance following the disease As in other streptococcal infections it is probable that any protection afforded by an attack is transient Experimentally Gay and his colleagues[1] have called attention to the role of mobilized clasmatocytes in the prevention of streptococcus infections and in establishing a condition of enhanced resistance

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CHAPTER I-A

VINCENT'S ANGINA

BY ARTHUR L. BLOOMFIELD

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Under the general heading of Vincent's angina are included a variety of inflammatory lesions of the buccal cavity and pharynx, acute or subacute, localized or widespread, ulcerative or membranous, associated with the presence of spirilla and fusiform bacilli. Similar organisms may be found at times in necrotizing lesions elsewhere in the body, but the present discussion concerns itself primarily with the cases in which the seat of the trouble is in the mouth or throat. Vincent's angina is to be thought of as a syndrome rather than as a specific disease.

ETIOLOGY

Predisposing Causes

These are ill-defined. *In civilian practice sporadic cases are seen without obvious relation to age, sex, season or the general condition of the patient.* We have observed a number of instances in healthy medical students and nurses who were *physically fit and who had had no recognized contact with the disease.* Epidemics were frequent, however, in military units during world war I (trench mouth)

and here as well as in certain outbreaks which have been described in groups of civilians the greatest incidence is said to be in the late winter and early spring months The condition of the teeth and gums in our experience bears no definite relation to susceptibility to the disease although other observers hold a contrary opinion and feel that pyorrhea is an essential predisposing factor Ulcerative or membranous lesions in the buccal cavity associated with the presence of spirilla and fusiform bacilli may occur in diseases such as leucemia agranulocytosis and infectious mononucleosis The significance of such findings as will be pointed out below is not clear

Exciting Causes

The organisms were described first by Plaut in 1894 in membranous tonsillitis and Vincent shortly thereafter emphasized the syndrome with especial reference to its resemblance to diphtheria A tremendous amount of bacteriological study has been devoted to the subject the general results of which indicate that the spirilla and fusiform bacilli found in the disease represent groups of bacteria rather than highly specific types The bacillus fusiformis is from 4 to 14 micra long and about 0 5 micron wide at its center from which it tapers to the ends It is anaerobic non motile non spore forming gram negative and stains readily with the usual dyes Cultivation is not difficult if anaerobic methods are used The spirilla (*Borellia vincenti*) have from 5 to 8 wide convolutions the ends are pointed they are motile gram negative and stain less readily than the fusiform bacilli Controversy still exists as to the exact life cycle of these organisms whether they are entirely distinct or whether they represent different forms of a single parasite A minute filterable form has been claimed to exist

It is generally known that spirilla and fusiform bacilli indistinguishable from those present in disease are found in healthy people although this statement must be modified to the extent that the organisms usually are associated with a tissue abnormality They may for example abound in ill kept mouths especially in the pus of pyorrhea alveolaris or in the crypts of tonsils as well as in more distant localities such as the external genitalia The entire subject has been carefully reviewed by Davis and Pilot who also discuss unsuccessful attempts to produce experimental lesions in rabbits with pure cultures of these organisms although material contaminated with pyogenic cocci resulted in putrid suppurations In view of this wide distribution among healthy people it is not surprising to find that many lesions in the respiratory passages and elsewhere may be associated with the presence of fusiform bacilli and spirilla and they have been found in mercurial stomatitis in gangrenous naso-pharyngitis in pulmonary suppurations in genital lesions and in a variety of other conditions

This ubiquity has led many observers to believe and with reason that the

Vincent s organisms are essentially opportunistic and that they are usually to be regarded as secondary invaders although they may play an active part in the promotion of putrid or gangrenous processes along with other microorganisms Their relation to the clinical entity Vincent s angina will be discussed later in this article

As far as we know the group of bacilli and spirilla under discussion does not occur outside of the human body except on material freshly contaminated from human sources Hence conveyance of the disease if it be caused by these organisms is probably by direct contact with the patients or with recently contaminated objects To what extent autogenous infection with bacilli and spirochetes, already present in the patient plays a part is not known definitely

Further Considerations in Regard to Etiology

As we pointed out above the exact cause of the clinical entity of Vincent's angina and the allied conditions which are associated with the presence of spirilla and fusiform bacilli has never been determined definitely The constant presence of these organisms does to be sure suggest that they are the cause of the lesions but inasmuch as exactly similar microbes may be found in healthy people and in a variety of disorders which are definitely due to other agents the nature of the relationship is open to question Modern opinion tends in the direction of regarding the Vincent s organisms as secondary invaders which unfold their activity on soil damaged by other agents Our own opinion is that we have no evidence that fusiform bacilli and spirilla are the primary and essential cause of the clinical entities included under Vincent s angina This opinion is based partly on the observation of a case which seems of sufficient importance to be quoted in some detail

The patient (L H 156 907) was a man of fifty years who entered the clinic complaining of sore throat swollen eyes fever and night sweats There was no history of any similar previous attack and he had always been strong and vigorous and had done outdoor work About two weeks before entry his throat became sore and fever developed During succeeding days he became generally worse and the entire mouth became involved Three days before entry he woke up with sore eyes which became rapidly worse and discharged yellow pus

On examination he was a well nourished man evidently in great discomfort The conjunctivae were intensely injected and there was an abundant purulent discharge The breath was foul and the entire mouth cavity including tongue gums and lips was covered with a thin greenish white semi translucent membrane interrupted here and there by superficial ulcerations which bled freely The nose was clear There were moderate swellings at the angles of the jaws which were not tender Physical examination otherwise was negative The

and here as well as in certain outbreaks which have been described in groups of civilians, the greatest incidence is said to be in the late winter and early spring months. The condition of the teeth and gums in our experience bears no definite relation to susceptibility to the disease, although other observers hold a contrary opinion and feel that pyorrhea is an essential predisposing factor. Ulcerative or membranous lesions in the buccal cavity associated with the presence of spirilla and fusiform bacilli may occur in diseases such as leucemia, agranulocytosis and infectious mononucleosis. The significance of such findings, as will be pointed out below, is not clear.

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This ubiquity has led many observers to believe, and with reason, that the

ganisms were secondary invaders in the mouth without penetrating to the conjunctivae and that the common cause of both stomatitis and conjunctivitis was some other agent of unknown nature Clinically this was a typical instance of Vincent s stomatitis and the findings lend support to the view already held by many that the fuso spirillary infestation is a secondary invasion

The whole status of the problem may then be summarized as follows Vincent s organisms exist as widespread saprophytes in healthy people they occur probably as secondary invaders in a variety of clinical lesions including those of Vincent s angina The latter should be regarded as a syndrome rather than as a specific disease The primary agent or agents responsible for Vincent s angina if the above assumptions are correct is as yet unidentified

Symptomatology

While the cases may be divided into those showing localized ulcerating or membranous lesions in the tonsillar region and those with a more diffuse gingivitis or stomatitis it must be remembered that all gradations from one type to the other may occur With regard to severity especially of the constitutional symptom there is also the greatest variation Some patients may present severe ulcerating lesions with little fever and only slight departure from normal well being others are profoundly intoxicated and have a sharp febrile reaction

The case of average severity begins with the general constitutional reaction of an acute infection headache malaise general aching and perhaps chilliness and nausea This is followed soon by distress due to the local lesion burning and pain if gingivitis and stomatitis are present pain on swallowing if the lesion is confined to the tonsil The findings apparent locally are as follows

The Tonsillar Form

Hand in hand with redness and swelling of one or occasionally both tonsils and adjacent pillars there appears a dirty grey or yellowish membranous exudate This often takes the form of a thick pultaceous mass which may have a depre sed appearance owing to ulceration or necrosis of the underlying tissues The margins of the lesions may be discrete and marked by a border of exaggerated redness We have seen a number of small lesions become confluent and the process while usually localized may spread widely over the adjacent parts into the naso-pharynx or buccal cavity The membrane may be detached to some extent but usually reforms The breath has the peculiar typical stinking odor associated with lesions in which putrefactive anaerobes are present Once familiar with this smell one never forgets it The glands at the angles of the jaws usually are enlarged and tender sometimes they reach huge proportions

temperature varied from 101° F to 103° F and the pulse was moderately accelerated The urine was clear The Wassermann test was negative R B C 5 000 000 W B C 13 000 with 74 per cent polymorphonuclears On the day after entry his condition seemed worse He was extremely uncomfortable, and it was practically impossible for him to swallow The membrane in the mouth was adherent and on attempts at removal there was free bleeding During subsequent days the areas devoid of membrane became covered with purplish red granulations which bled very easily The eyes presented the picture of intense conjunctivitis The bulbar conjunctivae had the appearance of red plush and there was slight chemosis The lids became moderately edematous and swollen, and there was a very profuse yellow discharge

Bacteriological studies showed the following Smears from the mouth showed a predominance of typical fusiform bacilli and spirilla such as are seen with Vincent's stomatitis Cultures from the mouth gave streptococci and white staphylococci Cultures from the ocular conjunctivae yielded no growth, but the pus from the eye showed some white staphylococci and streptococci Repeated smears of scrapings from the conjunctivae at no time showed fusiform bacilli or spirilla

Treatment consisted of cocain and silver nitrate to the eyes with frequent irrigations intravenous injections of neoarsphenamine and of antimony potassium tartrate The mouth was kept as clean as possible by saline irrigations which were followed by applications of Fowler's solution For the first four days after admission there was little change in his condition From this time on however there was gradual improvement with falling temperature The membrane in the mouth seemed to resolve leaving a slightly bleeding ulcerated surface which became covered with flat purplish granulations These in turn gradually took on the appearance of the normal mucous membrane The conjunctivitis too gradually subsided over a period of two weeks At no time did the mucous membrane of the anterior nasal passages show changes

In the case herewith reported there can be little doubt but that the stomatitis and conjunctivitis were due to a common cause Their coincident occurrence and subsidence and the intense character of the ocular inflammation which could be explained on no other grounds clinical or bacteriological all point to this conclusion A consideration of the literature both on Vincent's stomatitis and on conjunctivitis was barren in this connection save for an undocumented statement that with Vincent's angina the eyes are occasionally hyperemic' (Amer Encyc and Dict of Ophthalmology, vol 18 p 13578 Chicago 1921)

If the assumption is correct that the stomatitis and conjunctivitis in this case were due to a common cause it is equally certain that no spirilla or fusiform bacilli could be found in the discharges from the eye or in scrapings from the conjunctival surfaces The obvious implication is that the Vincent's or

Diagnosis

The appearance of the diffuse gingival and buccal forms is characteristic and the diagnosis may be possible at a glance The localized tonsillar forms are to be distinguished from streptococcic tonsillitis diphtheria and syphilis While one may describe textbook differences our experience has been that careful bacteriological study is necessary to make a definite distinction between these conditions Vincent s organisms may be found in a variety of conditions and their mere presence does not complete the diagnosis One should always be sure that there is not some underlying disease such as leucemia In doubtful cases where syphilis is suspected the Wassermann reaction is important, and the therapeutic test may be tried although arsphenamine administration sometimes is followed by clearing up of non luetic Vincent s lesions The loughs after tonsillectomy usually contain the Vincent s organisms

Prognosis

The outcome usually is favorable even after a prolonged course Occasional fatal cases with sepsis occur Death always raises the question of whether the diagnosis has been correct and whether the lesions have not been associated with some other disorder such as leucemia or agranulocytosis We have seen one fatal case which appeared to be a straightforward one of Vincent's angina

Prophylaxis

Inasmuch as fusiform bacilli and spirilla are found in tonsil crypts and in the peridental spaces if pyorrhea is present careful mouth hygiene and regular dental attention as well as tonsillectomy have been advised as prophylactic measures Certainly such precautions even if these organisms are the fundamental cause of the disease do not confer an absolute protection since the condition may occur in clean and well kept mouths

The sporadic cases of civil life do not seem to be a great menace to the attendants and I have never seen an instance of the disease arising by direct contact under these conditions None the les precautions should be taken the discharges from the mouth should be destroyed and the utensils and linen sterilized Attendants in close contact should wear gowns and wash the hands thoroughly after handling the patient In situations in which Vincent s stomatitis is likely to supervene as in bichloride of mercury poisoning penicillin (see under Treatment) may be of value as a prophylactic

The disease may last from one to several weeks and recovery is heralded by fall in temperature loosening and shrinking of the area of exudate and improvement in the local symptoms The affected mucous membrane remains red and tender for some time

The fever may be slight or may rise to high levels Usually there is a continuous pyrexia with moderate irregular dips The pulse is elevated in the toxic cases In very ill patients there may be profound prostration

The Buccal Form

In this type of the disease a more superficial diffuse process is present affecting especially the gingival regions although the tongue and mouth in general may be involved An intense erythema of the parts is followed soon by shallow, superficial ulcerations covered by a thin almost translucent, grey membrane The gums are swollen there is salivation the teeth may be loosened and intense discomfort may make it difficult for the patient to take food or even fluids The regional nodes are swollen and the constitutional reaction is often severe with high fever for one or more weeks The process resolves by desquamation of the exudate leaving a red sensitive surface which gradually becomes normal

Transitional forms between the two types and every grade of variation in severity of the local lesion and of the general reaction are encountered There may be recurrences after healing apparently has set in and months may elapse before the patient is entirely well

LABORATORY FINDINGS

Spirilla and fusiform bacilli usually are readily demonstrated in stained smears of scrapings from the lesions Many other bacteria naturally are present as well The urine may show the findings of a febrile disease The red blood cells usually are not reduced occasionally a moderate anemia may develop Moderate leucocytosis (10 000–15 000) is the rule with a slight polymorphonuclear increase The border line between Vincent's angina and the agranulocytic anginas with leucopenia is not clearly defined

COMPLICATIONS AND SEQUELAE

Complications are for the most part due to an exaggeration of the local process with extensive necrosis and sloughing There may be permanent scars, local abscesses usually due to pyogenic bacteria may form and occasionally a general blood stream invasion perhaps by streptococci, may take place Convalescence often is prolonged and the patient may be weak and below par for months

Diagnosis

The appearance of the diffuse gingival and buccal forms is characteristic and the diagnosis may be possible at a glance The localized tonsillar forms are to be distinguished from streptococcic tonsillitis diphtheria and syphilis While one may describe textbook differences our experience has been that careful bacteriological study is necessary to make a definite distinction between these conditions Vincent s organisms may be found in a variety of conditions and their mere presence does not complete the diagnosis One should always be sure that there is not some underlying disease such as leucemia In doubtful cases where syphilis is suspected the Wassermann reaction is important and the therapeutic test may be tried although arsphenamine administration some times is followed by clearing up of non luetic Vincent s lesions The sloughs after tonsillectomy usually contain the Vincent s organisms

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The sporadic cases of civil life do not seem to be a great menace to the at tendants and I have never seen an instance of the disease arising by direct contact under these conditions None the less precautions should be taken the discharges from the mouth should be destroyed and the utensils and linen sterilized Attendants in close contact should wear gowns and wash the hands thoroughly after handling the patient In situations in which Vincent s stomatitis is likely to supervene as in bichloride of mercury poisoning penicillin (see under Treatment) may be of value as a prophylactic

Treatment

The disease is not to be regarded lightly and if fever is present the patient should be kept in bed and the general measures used in acute infectious diseases are in order Fluids should be forced if necessary parenterally The problem of feeding may be a difficult one if the lesions cause so much pain that the patient refuses to eat However small amounts of concentrated liquid nutriment usually can be taken For the distress and restlessness incident to the infection sedatives and analgesics are indicated Codein the bromides amytal and if necessary morphia may be used

Every conceivable local application has been advised In the writer's experience intensive cleansing of the affected parts especially in the diffuse form is most important By means of small cotton swabs the exudate should be carefully wiped away avoiding undue trauma The surfaces may then be swabbed with Fowler's solution after which there should be a thorough rinsing and gargling with warm salt solution This process may be repeated two or three times a day Under this regimen most of our cases have cleared up satisfactorily although not necessarily until days or weeks have elapsed

Strong antiseptic washes are to be avoided where intense inflammation exists Among various applications which have been advised are two per cent sodium perborate arsphenamine in ten per cent solution in glycerine and two per cent gentian violet

Intravenous injections of arsphenamine have been recommended highly and used extensively The writer feels that this procedure should be restricted as far as possible to the treatment of syphilis and that because of the risk of reactions it is not usually justifiable in other conditions We have seen a number of cases of Vincent's angina that did not respond to intravenous arsphenamine although prompt recovery undoubtedly often takes place If used the dose should be small neoarsphenamine 0 or 0 3 gms If no result is obtained from the first injection further administration is not to be advised

The availability of penicillin has altered completely the therapeutic problem in Vincent's angina and stomatitis What was previously a stubborn and often intractable condition is almost always readily amenable to a few doses of the antibiotic If the intramuscular route is employed doses of 10 000 to 0 000 units given every 3 to 6 hours up to a total dosage of 100 000 to 200 000 usually suffices to effect a cure although longer and more intensive therapy may be necessary in some cases Within a few hours after the start of treatment the patient often feels much better "toxic" symptoms subside and fever if present, usually falls in 24 to 48 hours Spirilla may no longer be seen in smears after a few hours and the local lesion ceases to be painful and melts away in hours to days We have seen results little short of miraculous in some cases of desperate gangrenous

stomatitis and gingivitis associated with severe leucemia and mercurial poisoning in other patients the results were less striking but penicillin is certainly the treatment which should be tried first It is a question whether penicillin applied topically in a solution of 250 to 500 units per c c adds anything to the effect obtained by systemic therapy If penicillin is employed no violent local manipulations are necessary a gentle swabbing and cleansing of the lesions with pledgets soaked in warm normal saline solution and saline gargles are all that is necessary

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CHAPTER II

RHEUMATIC FEVER

By HOMER F. SWIFT and CURRIER McEWEN

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INTRODUCTION

Synonyms — Rheumatic fever acute rheumatism acute articular rheumatism inflammatory rheumatism polyarthritis rheumatica rheumatic infection rheumatic disease the rheumatic state acute rheumatic fever

As indicated above many names are in use for rheumatic fever several of which are unsuitable The modern concept of the disease as one affecting many structures has made obsolete those synonyms implying joint damage as the essential manifestation The list of suitable names has been further shortened by the exclusion of those implying acuteness for one of the important advances in the understanding of this malady has been the appreciation that it is by nature chronic The word rheumatism is vague as it has come through long usage to mean simply pain in or about joints which may have numerous causes Because the term rheumatic fever in the past has been associated in the minds of many physicians with a disease limited to the joints there has been a tendency in recent years to substitute for it the expressions rheumatic infection rheumatic disease or rheumatic state We believe however that rheumatic fever remains the preferable term and that efforts to clarify the problem should be directed toward a better understanding of the disease rather than toward the development of new terms

Definition — Rheumatic fever is a disease apparently infectious of undetermined etiology essentially chronic and recurrent in nature but often presenting acute phases it primarily attacks supporting tissue of mesenchymal origin together with the adjacent mesothelial membranes and is made manifest by a toxic state characteristic involvement of the cardiovascular system polyserositis arthritis subcutaneous nodules and chorea A further peculiarity is the marked response of the fever acute toxic state and polyarthritis to certain drugs

Incidence

Because rheumatic fever is reportable only in Norway Denmark and Iceland it is impossible to obtain more than an approximate idea of the incidence in various countries The difficulty is enhanced by the marked difference in relative frequency and in clinical manifestations in various climates In Denmark Warburg (1931) estimated a gross rate of about 20 per 10 000 per year in the period from 1890 to 1930 In Norway between 1926 and 1930 Motzfeldt (1934) reports an incidence of 10 7 per 10 000 per year with a variation between 21 4 in the region of Bergen and 8 4 in Oslo Edstrom (1935) calculates similar frequencies in various parts of Sweden with official rates varying between 11 6 per 10 000 per year in Gotenburg to probable total rates of 25 to 30 per 10 000 in the entire population of the same city It is interesting to note that the lowest per cent incidence was in the northernmost region of Sweden

In this country a number of approximate estimates have been made by indirect methods Thus on the basis of mortality figures Swift (1931) calculated that there were approximately 167 000 cases of rheumatic fever in the United States in 1916 and about the same number in 1923 these figures however do not include patients with inactive rheumatic heart disease According to an estimate derived by Paul (1930 a) from a study of the incidence of cardiac valvular disease among school children drafted men hospital patients and insured persons the total number of cases of rheumatic heart disease in a population of 100 000 000 would be about 840 000

Another means of estimating the incidence of the disease is the study of hospital admissions It has been stated that patients with rheumatic polyarthritis make up 3 to 7 per cent of such admissions to large general hospitals in the United States and Europe with a much lower rate in cities situated in the southern part of this country (Seegal and Seegal 1927) Among 5 799 patients admitted to the Adult and Children s Medical Services of the New York University Division of Bellevue Hospital during 1935 4 3 per cent entered because of some manifestation of active rheumatic fever including active carditis and 1 6 per cent because of inactive or questionably active rheumatic heart disease a total of 5 9 per cent due directly or indirectly to rheumatic fever

The seriousness of rheumatic fever can be estimated better from the demonstration that diseases of the heart are the greatest cause of death today and that over 25 per cent of these cases are of rheumatic origin as shown by Wyckoff and Lingg (1926) in an analysis of 1 051 cases of heart disease in New York City When in addition it is realized that the victims of the disease are preponderantly under forty years of age or in other words are individuals who normally should have their most productive years still before them one can readily understand its great economic and social importance

The incidence of rheumatic fever would be increased greatly if rheumatoid arthritis were included in this category However although considerable evidence is accumulating to suggest a relationship between these two clinical entities (Dawson and Tyson 1936) the facts do not yet warrant such an inclusion from the standpoint of vital statistics

In spite of its seriousness the problem presented by rheumatic fever has its brighter aspect because the incidence of the disease apparently is diminishing Thus the admission rates for the disease in the British and American Armies fell 60 and 82 per cent respectively over a twenty year period (Swift 1931) This decreasing rate is further indicated by data from the Metropolitan Life Insurance Company which show a fall in the

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part but the relative importance of each one has not yet been determined with certainty

Age — The influence of age upon rheumatic fever is very great for not only are children chiefly affected but also the manifestations of the disease which one may expect in a given case are governed largely by the age of the patient This latter characteristic of rheumatic fever is discussed more fully under *Symptomatology* Analyses by many different investigators indicate that the great majority of first attacks occur between the ages of five and twenty years The median in New York City according to the figures of De Graff and Lingg (1935 a) is at fourteen years and the mode at nine ten and eleven years in this country and England the highest incidence of first attacks occurs in the age period from eight to ten while in continental Europe and in the Scandinavian countries the peak is between sixteen and twenty years (Edstrom 1935) These differences may account in part for the relatively greater incidence of chronic arthritis following rheumatic fever that is reported by European clinicians However first attacks may occur in any age period Rheumatic fever rarely occurs in infants in the reported cases the mothers usually have been suffering from an acute phase of the disease suggesting the factor of contagion (Andrieu 1936) The possibility of intrauterine transmission from mother to child has been raised by reports of a few instances of the disease in the child of an acutely ill rheumatic mother within a few hours of birth (Andrieu 1936 Richdorf and Griffith 1936)

ENVIRONMENTAL FACTORS — These are numerous but many of them such as the effect of poverty and occupation housing urbanization malnutrition and exposure to vermin may all be discussed under the general heading of *Social Condition* Considerable evidence indicates that poverty and rheumatic fever are associated Glover (1930) in England states that No disease has a clearer cut social incidence than acute rheumatism which falls perhaps thirty times as frequently upon the poorer children of the industrial town as upon the children of the well to do Paul Harrison Salinger and DeForest (1934) confirmed this tendency in New Haven Connecticut and found rheumatic heart disease eight times more prevalent among children attending a public school in a poorer urban district than among those attending a private school As pointed out in an investigation conducted by the Medical Research Council of Great Britain (1927) the high incidence among the poor probably is due to the malnutrition dirt crowding and other bad hygienic conditions following in the wake of poverty In the same way poorly paid occupations the crowded sections of industrial cities unsatisfac

annual death rate for valvular heart disease from 64 per 100 000 in 1921, to 45 per 100 000 in 1930 (Dublin and Lotka 1937)

Etiology

The discussion of etiology of a disease the causative agent of which is unknown must necessarily be unsatisfactory However there are a number of predisposing factors about which much of value has been learned, and certain of the more important theories as to the exciting cause must be discussed

Predisposing Factors

The factors predisposing to rheumatic fever may be conveniently discussed under the headings personal environmental and infectious

PERSONAL FACTORS — The personal influences usually considered are those of race sex family and age Of these the data concerning racial susceptibility to the disease still are too vague to warrant discussion here and sex does not seem to play a very important role save in the case of chorea which occurs about two and a half times more frequently in girls than in boys The influences of family and age however require more detailed presentation

Familial Tendency — There is much evidence that rheumatic fever is a familial disease and that in this respect it is very similar to tuberculosis Campbell and Warner (1930) in an analysis of two hundred and fifty children with rheumatic fever found that 60 per cent gave a history of present or past rheumatic fever in other members of the family whereas in a control group of children suffering from other diseases only 20 per cent gave a rheumatic family history Similar results had been obtained by St Lawrence (1922) and by Faulkner and White (1924) and others This familial tendency may theoretically be dependent upon three different factors an inherited susceptibility to rheumatic fever the common action upon all members of the family of certain environmental conditions which favor the disease a direct spread of infection from one member to another Recent data reported by Wilson and Schweitzer (1937) suggest that the familial tendency is due to inherited susceptibility transmitted as a single autosomal recessive gene Paul and Salinger (1931) have stressed the importance of the infectious factor by demonstrating that attacks of rheumatic fever often are associated with non specific infections such as colds and sore throats in other members of the immediate family It is probable that all three factors play some

camps were preceded by epidemics of tonsillitis with the peak of the latter two to three weeks prior to that of the rheumatism Similar epidemics are reported by Coburn (1935 a and b) and several are reviewed by Paul (1930) Coburn noted that influenza pneumonia and chicken pox did not induce recrudescences of rheumatic activity in a group of convalescent rheumatic children while on the other hand hemolytic streptococcal respiratory infections did precede severe recrudescences By carefully recording the illnesses in all members of several rheumatic families Paul and Salinger (1931) showed that apparently non specific infections such as tonsillitis otitis media and colds in certain siblings or parents were chronologically related to attacks of rheumatic fever in others This suggested that a common etiologic agent was spreading through these families and making itself manifest differently in different individuals

Wilson and her coworkers (1935 a and b) on the other hand did not observe such close relationships Probably a fairly representative picture is that given by Edstrom (1935) who analysed the data in Lund Among eight hundred and fifty cases of polyarthritis rheumatica studied during the period 1911–1933 there was a preceding acute tonsillitis in 41 per cent other acute upper respiratory infection in 24 per cent miscellaneous non respiratory infection in 6 per cent and no history of any antecedent infection in 29 per cent This author notes that similar relationships were found by Motzfeldt in Norway Kuttner (1937) and Duckett Jones have seen mild relapses in children under careful observation without any evidences of respiratory infection Coburn feels that many prodromal respiratory infections are too mild to be noted by the patients and that careful bacteriological studies are required before the possibility of these mild infections can be surely eliminated

Theories Regarding an Infectious Agent

While the exciting agent in rheumatic fever has not been conclusively demonstrated the various theories advanced must be considered for it is possible that from some of them the correct answer to the puzzling problem eventually will be obtained

Miscellaneous Microorganisms —The attributing of etiological roles to Gram negative anaerobic bacilli (Achalme 1891) and staphylococci (Singer 1898) are chiefly of historic interest The more recent implication of tubercle bacilli in the picture (Reitter and Lowenstein 1930) has failed of confirmation Streptococci on the other hand long have claimed the serious attention of investigators in this field The earlier

tory housing and vermin are other factors associated with poor general health and the easy spread of infection It is obviously difficult to analyze any of these factors alone since the action of each is related to the others

Geographic Distribution — It has long been emphasized that rheumatic fever is rarely seen in the tropics and Clarke (1930) has even gone so far as to deny the occurrence of the disease among people who have never lived outside the true tropics In the United States studies such as those of Seegal and Seegal (1927) have shown that the yearly admissions for rheumatic fever to a selected group of hospitals decrease as one goes from the northern to the southern states In surveying the incidence of rheumatic valvular disease among Indian school children in different reservations situated in northern middle and extreme southern portions of the United States Paul and Dixon (1937) found the rates to be 4 5 1 9 and 0 5 per cent respectively Reports (Coburn 1931 and Jones and coworkers 1937) of the improvement in rheumatic children transported to tropical or subtropical regions is confirmatory evidence of the influence of climate On the other hand in both Norway and Sweden the incidence of the disease is smaller in the most northerly provinces Informed observers report that rheumatic fever is extremely rare in Greenland

Meteorological Influences — Rheumatic fever is like most other infectious diseases in having a definite seasonal trend In the United States and most of continental Europe the incidence rises in the late winter reaches a peak in the spring and then decreases gradually to a low point in the fall (Sutton 1928) In England on the other hand the curve is almost exactly the reverse The reasons for these differences in England and the United States and in a single country at different times of year are not clear They have been shown to reflect the incidence of upper respiratory infections (Glover 1930 Coburn 1931) and Rinehart (1935) has pointed out that the peaks of the curves follow periods of proportionately little sunshine

Other atmospheric conditions thought to predispose to rheumatic fever are those associated with combined cold and dampness inhabitants of maritime cities especially those living along waterfronts or old water ways seem more prone to rheumatism than those living in more continental climates Possibly this is due to the greater incidence of certain types of upper respiratory infections

General Infection — Most students of this disease consider infections especially those of the upper respiratory tract of significance in the etiology of rheumatic fever and for over a century there have been recorded observations indicating these relationships For example Glover (1930) showed that two outbreaks of rheumatic fever in military training

TABLE 1 Serological Differentiation of Hemolytic Streptococci into Specific Groups and Types

HEMOLYTIC STREPTOCOCCI

Serological Groups

Determined by Specificity of Carbohydrate C

	Group A	Group B	Group C	Group D	Group E	Group F	Group G	Group H	Group K
Probable Normal Habitat	*Man* Scarlet fever Puerperal Erysipelas Sore throat etc Carriers	*Cattle* Mastitis Normal milk	*Horses* Strangles Endometritis *Cattle* Mastitis *Guinea pigs* Adenitis *Monkeys* *Many animals*	*Cheese*	*Normal milk*	(Minute streptococci) *Man* Resp tract Intestine Vagina	(Some minute streptococci) *Man* Resp tract Intestine Vagina *Monkeys* Resp tract Skin *Dogs* Otitis	*Man* Resp tract Intestine	*Man* Resp tract
	Secondary Habitat *Cattle* Mastitis *Laboratory animals*	*Possible Secondary Habitat* *Man* Throat Vagina	*Man* Skin Throat Vagina	*Man* Intestine Vagina					
	More than 30 serological types known *Type specific* protein M	Many serological types Type specific polysaccharide S	Types known to exist but not completely studied in Groups C to I						

reports of Triboulet (1897) Westphal Wasserman and Malkoff (1899) and Poynton and Paine (1900) failed to be convincing possibly in part due to the imperfect knowledge of identification and classification of streptococci three decades ago Doubt has been thrown upon the significance of the more recent reports of Small (1927) and Birkhaug (1927) and of Cecil Nicholls and Stainsby (1929) concerning the possible etiological role of indifferent or green forms by the work of Lichtman and Gross (1932) Collow (1933) and McEwen Alexander and Bunim (1936) all of whom showed that with similar methods these varieties of streptococci could be recovered from patients suffering from non rheumatic diseases

Hemolytic Streptococci — Within the past decade the possible etiological significance of hemolytic streptococci has been gaining ground steadily, due in considerable degree to the part these microorganisms play in the prodromal infections Investigations along these lines have been greatly facilitated by the establishment of a valid immunological classification (Lancefield) of the hemolytic streptococci in general and of the human pathogens in particular (Lancefield 1928 1933 Griffith 1934)

The demonstration of numerous immunologically definable groups of streptococci which may be recovered from man is outlined in Table I Obviously the mere recovery of hemolytic streptococci in cultures from various parts of the body does not necessarily establish their etiological role in a given disease Most human streptococcal infections are caused by members of Group A although members of other groups can assume pathogenic roles under special circumstances

Because many recent investigations concerning the reaction of the body to hemolytic streptococci have to do with various types of immune responses it is necessary to have some understanding of the factors involved Table II shows the different antigens and the corresponding antibodies so far recognized

Obviously several possibilities exist in respect to antigenic function as well as to antibody response in streptococcal infections Some strains are strong and others weak erythrogenic toxin producers the same holds for hemolysins so called streptolysins and for fibrinolysins (Hadfield Magee and Perry 1934) These antigens elaborated into the culture media are studied easily Comparably wide variations are known to exist among streptococci in their content of intrabacterial antigenic components and also in the responses of animals inoculated with Group A hemolytic streptococci It should be noted that the only antibodies elaborated in response to Group A hemolytic streptococcal infection or immunization which have type specific significance are the anti M

in their sera have been confirmed repeatedly but most observers agree that such high titres characterize recent hemolytic streptococcal infections rather than rheumatic fever for many non rheumatic individuals have comparable concentrations In investigating this question more minutely Coburn and Pauli recorded that streptococci isolated in the prodromal period from their patients who subsequently suffered an attack of rheumatism produced in vitro more erythrogenic toxin and streptolysin than did strains isolated from rheumatic patients who did not subsequently develop rheumatic fever They (1935 f) thus concluded that infection with toxin producing strains of hemolytic streptococci initiates a process peculiar to rheumatic subjects during which a substance is released presumably from the antibody producing tissues which either directly or indirectly alters mesodermal structures the release of this toxic substance seems to take place only when there is an immune response to hemolytic streptococci Several observers on the other hand have not found such close correspondence between antibody production on the part of the patient and the onset of rheumatic symptoms For example Wilson and coworkers (1935 a and b) found none at all Mote (1937) found antistreptococcal immune bodies in only about half of his patients and McEwen Bunim and Alexander (1936) could detect no constant relationship between concentration of group specific precipitins or antistreptolysins and the onset of rheumatic manifestations Swift and Hodge could detect no significant rise in antistreptolysin titre in between 15 and 20 per cent of their patients with definite hemolytic streptococcal infections

Such data raise the question as to whether there are any differences in immunological responses in the two classes of patients who contract hemolytic streptococcal infections the one suffers no subsequent rheumatic fever the other develops the disease In one respect we have found the two groups to differ in general the non rheumatic group develops strong titres of type specific antibodies anti M precipitins earlier than do the rheumatic (Swift and Hodge 1936) Those rheumatic patients who had relatively short and mild attacks had good concentrations of anti M precipitins early while those with prolonged low grade rheumatic fever showed similar strong titres only late or not at all In his latest report on this subject Coburn (1936) notes that his rheumatic patients were slower in developing high concentrations of both anti streptolysins and anti M precipitins than were the non rheumatic patients with hemolytic streptococcal infections If the foregoing findings the only investigations of this nature so far reported are corroborated there is a suggestive clue as to how the rheumatic patient behaves toward hi

TABLE II

Antigenic Factors in Group A Hemolytic Streptococci		
In Bacterial Cell		*Antibodies*
Nucleoprotein (P)	In all streptococci pneumococci staphylococci etc	Anti P — not specific
Carbohydrate (C)	Common to all Group A streptococci	Anti C — Group specific
Protein (M)	Type specific substance	Anti M — Type specific
Toxin (Parker)	Dissolved from cell with difficulty	? ?
Elaborated into Surrounding Medium		
Erythrogenic toxin (Dick)	Varying amount by different strains	Rash blanching (in vivo)
Streptolysin	Varying amount by different strains	Antistreptolysin
Fibrinolysin	By many members of Group A By occasional members of Groups C & G	Antifibrinolysin
Leucocidin	(little investigated)	Antileucocidin
(Probably others)		

precipitins (Lancefield 1928) or the type specific agglutinins (Griffith, 1934) The presence of the other antibodies above mentioned signifies that they probably have been induced by Group A streptococcal infections but the anti P precipitins may denote the action of more remotely related bacteria

The previously discussed relationship between upper respiratory infection and rheumatic fever frequently is distinguished by the following sequence initial respiratory infection latent period of from a few days to several weeks then the appearance of rheumatic symptoms The immunological responses during the initial infection and latent period have been studied most extensively by Coburn and Pauli (1932 1935) who at different times have attributed different significances to the various phenomena observed They as well as others noted that so called anti P precipitins often appeared in the serum of rheumatic patients about the time of onset of rheumatic symptoms hence the suggestion that an antigen antibody response might account for the pathological processes much as the manifestations of serum disease have been explained More extensive studies however have tended to invalidate this hypothesis Similar investigations have shown no parallel relationship between the presence of Group A anti C precipitins and rheumatic symptoms

The original demonstration of Todd (1932 b) that most patients with active rheumatic fever have abnormal concentrations of antistreptolysins

reaches such a degree that the bacterial products are effectively made harmless then recovery occurs We thus may think of the manifestations of an infection at any given period as being due to the algebraic sum of the various injurious substances elaborated by the microorganisms together with the relative amount of true immunity and of hypersensitivity to those injurious substances

It seems probable that rheumatic patients who have suffered prodromal streptococcal infections have developed certain types of immunity to the infectious agent for they show relatively few positive Dick reactions Also they usually show high concentrations of antifibrinolysins and antistreptolysins even though they may possibly develop the latter more slowly than normal We consider the development of a high degree of type specific immunity of great importance for successful antibacterial immunity as contrasted with antitoxic The evidence so far available indicates that many rheumatic individuals who harbor hemolytic streptococci are slower in developing type specific immune bodies *than are non rheumatic patients and also that the degree of this type* specific immunity runs roughly parallel with tendency towards recovery In other words we may think of one of the factors in the rheumatic subject as a tendency towards the development of a chronic type of streptococcal infection with only partial immunity

Filterable Virus —The failure to establish conclusively the etiological role of bacteria in such an apparently infectious disease as rheumatic fever has caused many investigators to assume that an unknown virus is the causative agent Graff (1936) in Germany has been most vocal in this respect and has advanced numerous ex cathedra arguments in favor of a virus etiology For many years we have tested this hypothesis and applied most of the techniques commonly used in studying virus diseases We have injected most of the animal species usually employed for this purpose and have used various routes and many different materials obtained from rheumatic subjects both during the active stages of the disease and postmortem None of these investigations have yielded successful results We have examined also the cells in specific rheumatic lesions for intranuclear or intracellular inclusion bodies which if present would be strong presumptive evidence of filterable virus action but in none have such bodies been demonstrated incontestably

Theoretically from a histopathological viewpoint the evidence does not point towards virus action The site of injury inflicted by most viruses is primarily intracellular indeed these agents have been designated as obligate intracellular parasites In rheumatic fever on the other hand the primary injury appears to be on the intercellular collag

streptococcal infection, i.e., his effective type-specific antistreptococcal immunity is slower in developing than is that of the non-rheumatic.

In an attempt to explain still further the mechanism whereby injury is inflicted on the rheumatic subjects' tissues, the different ergic responses have been studied (Swift and coworkers, 1928 a and b; Klinge, 1933). Several sets of statistics indicate that cutaneous hypersensitiveness to streptococcal products is very marked among rheumatic patients, although it is also well established that comparable hypersensitiveness exists among non-rheumatic patients following hemolytic streptococcal infections (Coburn, 1931; Derick and Fulton, 1931). We (Derick, Hitchcock and Swift, 1930) have shown that animals are most easily sensitized to streptococci by focal infections with lowly virulent strains. Similar doses of the same strains given intravenously lead to a state of immune hypoergy (Swift and Derick, 1929). In other words, with the development of a satisfactory state of immunity the condition of hyperergy decreases. To carry over the analogy to the subject of rheumatic fever the following hypothesis is advanced. We conceive of two processes going on in an individual infected with streptococci, one tending towards the development of true immunity in which all of the harmful effects of the infectious agent are neutralized, the other tending towards the development of a hypersensitive state in which small amounts of the bacteria or of their products inflict abnormal injury on the hypersensitive tissues. Whether this latter state is beneficial to the whole animal economy by limiting the bacteria to a small localized zone is for the moment unessential. The important feature is the vulnerability of the tissues to traumatic agents, bacterial or physical. The subject who develops a good degree of immunity to an infection eliminates the infectious agent relatively quickly; the one who develops his immunity slowly tends to localize the microorganisms to certain areas where they survive and continue to infect the carrier. But the infection has not the features of the acute stages such as were manifest in the beginning; it has become chronic, and chronic infections are the types that lead to the highest degrees of bacterial hyperergy; witness the classical example of tuberculin hypersensitivity. The mechanism that tends toward the localization and encapsulation of the infectious agent without effectively eliminating it from the body may indeed furnish the most favorable circumstances for the continuation of the hypersensitive state, for this encapsulation may make the microorganisms less effective immunizing agents. It is not impossible that in these foci the bacteria are broken down in an abnormal manner and that from them products are thrown off that irritate instead of immunize. When and if true immunity

could detect neither curative nor prophylactic influence of high vitamin C intake in a group of rheumatic children

Pathology

General

Within recent times the tissue changes induced by the rheumatic infection have been studied extensively and out of a mass of apparently unrelated pictures has arisen a conception of the essential responses to the as yet undetermined noxious agent Admittedly it is difficult to detect much relationship between a swollen joint and warty growths on the cardiac valves and yet a definite relationship seems to exist and from an etiologic standpoint this was discussed for a century or more before the characteristic histopathological granuloma was described by Aschoff (1904) While recognition of the Aschoff body was an important advance in our knowledge of rheumatic fever too dogmatic a view concerning the necessity of making various rheumatic tissue changes coincide closely with this unit has at times tended to confuse rather than to clarify the picture Even Gross and Ehrlich (1934 a and b) most ardent advocates of the specificity of the Aschoff body have described at least seven forms which the various components of this body can assume and Gross and many other observers have described numerous nongranulomatous tissue changes which are attributable to rheumatic fever

It seems better therefore to give a general description of the histological tissue alterations and then see how these bring about the peculiar pathological pictures found in different organs at various stages of the disease

The primary injury apparently is inflicted on the supporting tissues derived from the mesenchyme and induces changes both in these supporting tissues and in the mesenchymal ground substance This ground substance (Hueck 1920) may be defined as a colloidal jelly like excretory product of the mesenchymal cells out of which is formed such supporting materials as the collagen and elastic fibres and the intercellular substance of cartilage and bone The injury of the collagen or elastica may vary all the way from focal necrosis with actual destruction of the fibres (Von Glahn 1927) to edematous swellings of the fibres in which the fibrils are pushed apart by mesenchymal ground substance infiltrate without definite interruption of their continuity (Klinge 1933) At the same time the focal swelling may result in compression of the neighboring fibroblasts This early eosinophilic infiltrate was long thought to be fibrin but because it sometimes fails to take all of the typical fibrin

enous ground substance. Admittedly much more must be known concerning the nature of viruses before such arguments can be used as final, but the negative results of animal inoculations are supported by histological findings.

Recently Schlesinger, Signy and Amies (1935) and Eagles and his coworkers (1937) have described some interesting investigations with small particles resembling the elementary bodies found in vaccinia and some other virus induced disease. These elementary-like bodies were obtained by high speed centrifugalization of exudates, cerebrospinal fluid, urine and ascitic fluid and in emulsions of nodules and arthritic tissues. These elementary-like bodies were agglutinated by the serum of patients with active rheumatic fever, chorea and rheumatoid arthritis. The relationship of the agglutinating capacity of these sera was rather bizarre and among all of the patients tested the capacity to agglutinate was about equally distributed between active and inactive rheumatic disease. However, among the patients whose sera were tested two or more times the agglutinating power was most marked both in frequency and intensity at the time of the most marked rheumatic activity. Such results throw considerable doubt on the true immunological significance of the reaction. It may be somewhat similar in nature to the reaction discovered by Tillett and Francis (1930) between the sera of active rheumatic patients, as well as in that of patients with pneumonia and the "C" substance of pneumococci.

In any event, more conclusive evidence must be advanced before a virus etiology of rheumatic fever can be accepted. Indeed Eagles and his collaborators think that this may be only one of a complicated group of factors. Certainly one must keep in mind the possible synergic role of bacteria and virus or of bacteria and other influences.

Vitamin Deficiency.—In this connection there should be mentioned the views of Rinehart and Mettier (1934) who described in the hearts of guinea pigs subjected to combined streptococcal infection and vitamin C deficiency lesions which they considered as similar to those occurring in rheumatic fever. On the basis of these findings and certain clinical features of the disease, such as its greater incidence among the poor and in seasons of less sunshine, Rinehart (1935, 1936) hypothesized that rheumatic fever may be a synergic result of infection and vitamin C deficiency. Others in repeating the experiments have considered the lesions in the guinea pigs less characteristically rheumatic but rather intensely scorbutic in nature (Schultz, 1936 a). Moreover, among our rheumatic patients Sendroy and Schultz (1936) could find no relationship between disturbed vitamin C metabolism and rheumatic manifestations, and Schultz (1936 b)

could detect neither curative nor prophylactic influence of high vitamin C intake in a group of rheumatic children

Pathology

General

Within recent times the tissue changes induced by the rheumatic infection have been studied extensively and out of a mass of apparently unrelated pictures has arisen a conception of the essential responses to the as yet undetermined noxious agent Admittedly it is difficult to detect much relationship between a swollen joint and warty growths on the cardiac valves and yet a definite relationship seems to exist and from an etiologic standpoint this was discussed for a century or more before the characteristic histopathological granuloma was described by Aschoff (1904) While recognition of the Aschoff body was an important advance in our knowledge of rheumatic fever too dogmatic a view concerning the necessity of making various rheumatic tissue changes coincide closely with this unit has at times tended to confuse rather than to clarify the picture Even Gross and Ehrlich (1934 a and b) most ardent advocates of the specificity of the Aschoff body have described at least seven forms which the various components of this body can assume and Gross and many other observers have described numerous nongranulomatous tissue changes which are attributable to rheumatic fever

It seems better therefore to give a general description of the histological tissue alterations and then see how these bring about the peculiar pathological pictures found in different organs at various stages of the disease

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are derived from primitive mesenchymal cells resting in the tissues As the lesion ages they contain relatively less cytoplasm they become longer lay down more and more collagen so that eventually they appear as typical fibroblasts In fact scar formation usually is the eventual fate of the rheumatic lesion and upon the amount of scarring depends the ultimate fate of the organ involved in the rheumatic process

The blood vessels in the neighborhood of a rheumatic lesion also show peculiar responses to the noxious agent New capillaries are formed quickly and the endothelium of the smaller veins and arteries become hyperplastic and cuboidal if the entire endothelium responds the vessel gives the appearance of a gland if only part responds there are crescentic areas of thickened endothelium These changes are different from the rheumatic vasculitis to be described later

Joints

The acutely involved joints show objectively the classical signs of inflammation swelling redness and local heat The first is due both to edema of the periarticular tissues and to infusion into the joints With recovery there is often a residual yellowish brown staining of the skin which is specially marked over the wrists and ankles The arthritic exudate consists of a turbid gray to yellow viscid fluid which coagulates quickly on standing The cellular content varies from a few hundred to forty five thousand or fifty thousand with an average from three thousand to ten thousand per cubic mm Early the predominating cell is the polymorphonuclear leucocyte with a few lymphocytes clasmatocytes and monocytes most exudates contain a varying number of cells with clear slightly eosinophilic cytoplasm and solid round pyknotic nuclei We have traced the involution of these cells through various stages and found them to be degenerated polymorphonuclears It is important not to consider them of erythrocytic origin for the presence of erythrocytes in any considerable number is indicative of severe trauma or of hemorrhagic tendencies Relatively few synovial cells are recognizable neither are large granuloma cells encountered In supravitally stained specimens McEwen (1935) found cells resembling young monocytes but with atypical and scanty mitochondria and neutral red bodies and considered them closely related to the primitive mesenchymal cells In the exudates of joints involved longer the proportion of polymorphonuclears is smaller and the clasmatocytes and lymphocytes increase often the clasmatocytes are filled with phagocytozed detritus and even with degenerated polymorphonuclears We have never found bacteria in these exudates

strains has been designated fibrinoid and to this peculiar early response to injury the general descriptive term fibrinoid swelling or infiltration early infiltrate (Klinge) has been applied The extent of fibrinoid swelling in a given lesion varies widely and depends somewhat upon the relative amount and concentration of collagen in the area attacked If it is loose and reticular the pink staining material may have a mesh like appearance if somewhat denser there may be a single minute mass of eosinophilic collagen and if more extensive as in an aponeurosis dense miliary masses of gelatinous material may be formed and ultimately, give rise to subcutaneous nodules which are seen easily

Quickly following the focal injury to the collagen there is also edema in the surrounding tissues this may be widespread such as is seen in acute polyarthritis or more localized in the case of subcutaneous nodules At this stage there are also numerous polymorphonuclear leucocytes scattered throughout the inflamed area These early responses are largely exudative in nature a fact that may be confirmed easily by observing an acutely inflamed joint and it seems highly probable that similar exudative reactions take place in viscera Indeed we have seen extensive exudates in the heart valves of patients who have succumbed early in an attack of rheumatic fever and Gross and his collaborators record numerous examples of exudative reactions in various cardiac situations especially near the conduction system Parenthetically it may be noted that the exudative responses to the rheumatic injury are the ones particularly affected by the antirheumatic drugs It seems improbable that the fibrinoid infiltrate is influenced by these remedies and it is almost certain that the later proliferative phenomena are not

Within a week or two Klinge thinks about two weeks of the time of primary tissue injury proliferative cells appear at the sites of the fibrinoid swelling These cells are irregularly square rhomboid or polygonal in shape and have a basophilic cytoplasm which is often irregular or ragged at the margins frequently there are basophilic cytoplasmic processes which seem to dip into the eosinophilic infiltrate as though the cells were attempting to fasten themselves in it The nuclei of these proliferative cells are vesicular with deep staining margins heavy nucleoli and densely staining masses of chromatin The proliferated cells in the myocardial and endocardial submiliary nodules often are large and polynuclear but in subcutaneous nodules the cells usually are mononuclear although polynuclear forms are seen sometimes

McEwen s (1932) investigation of these cells removed at biopsy from subcutaneous nodules and stained supravitally showed them not to be phagocytic like clasmatocytes or monocytes It seems probable that they

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A little later these areas of fibrinoid infiltration or focal necrosis are surrounded or invaded by typical rheumatic granuloma cells often they are arranged in spindles some polynuclear forms may be present so that in places the granulomata closely resemble myocardial Aschoff bodies Still later these cells become more and more elongated lay down increasing amounts of collagen until finally minute scars are formed

Similar granulomata in various stages of evolution are found in the periarticular ligaments aponeuroses musculotendinous junctions and in the areas where the tendons fuse with the periosteum in the neighborhood of rheumatic joints

Bursæ subjected to pressure such as those over the olecranon may show marked involvement so that the capsules may even become macroscopically thickened In the neighboring muscles often there is evidence of rheumatic myositis with granulomata which apparently arise in the perimysium and waxy degeneration of the contiguous muscle fibres Fibrositis and myositis are particularly noticeable in older patients and this fact doubtless explains the persistence of periarthritic pains in these individuals

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Subcutaneous Nodules

In subcutaneous nodules the various evolutionary and involutionary stages of the development of rheumatic lesions may be readily followed This has been systematically done by Mote Massell and Jones (1937) who compared the naturally occurring lesions with those induced in rheumatic subjects by subcutaneous injections of blood

Macroscopically lesions examined through intact skin are of differing consistency the youngest often are soft with ill defined surfaces which fuse into the surrounding tissue After a few weeks such nodules become harder and well circumscribed They then gradually decrease in size become less well defined so that the time of complete disappearance cannot be determined accurately Upon removal at biopsy the younger nodules are soft and jelly like in consistency while older nodules are firmer and have a translucent yellowish gray appearance not unlike sago granules

Microscopically the picture varies with the age of the nodule and the density of tissue involved In the earlier stages strands of altered collagen are separated widely by edema fluid which is often laid down as pink amorphous material through which may be sparsely scattered varying numbers of wandering cells In this stage the collagen injury usually takes the form of eosinophilic swollen strands although in some fibres there may be granular necrosis Blood vessels at the periphery show swollen endothelium and altered media Surrounding them and scattered through the nodule are collections of cells probably originating from resting mesenchymal elements and also some polymorphonuclears As the lesion ages the edema is less marked the altered collagen fibres are less widely separated and may take either eosinophilic or basophilic stains Blood vessels penetrate deeper into the nodules and many thick walled capillaries are seen the arterioles are lined with cuboidal endothelium which at times shows vacuoles The media is thickened and occasionally contains cells not unlike those lining the vessel At this stage the typical granuloma cells which appear to have evolved from the resting mesenchymal cells are most distinct They have the characters described earlier irregular shaped with basophilic cytoplasm and one or more nuclei with deep staining chromatin and heavy nucleolus They are often radially arranged about centers of injured collagen and may be so densely packed and numerous that a single group fills a low power microscopic field

Later stages are characterized by a gradual involution of the lesion towards a mass of fibrous tissue There is no evidence of edema the polyhedral basophilic cells become more elongated contain relatively less

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the fluid organizing exudates are left and give the picture of a thickened pleura If the processes have been slight the inflamed area may be covered again with a layer of smooth new formed mesothelium if extensive the fibrinous connections between the parietal and visceral pleura will be replaced by fibrous tissue with ultimate permanent adhesions between the two layers If the process is interlobar roentgenographic shadows of a thickened pleura may persist for weeks or months before they disappear

Pericardium — Rheumatic pericarditis is practically always secondary to carditis which so often is present near the site of egress of the great vessels at the base of the heart (Friedberg and Gross 1936) There is a desquamation of the mesothelial lining cells and a pouring out of serofibrinous exudate which is especially rich in fibrin If the process is limited to a small area healing may occur with a covering of the inflamed area with mesothelial cells which grow in from the edges If extensive the whole pericardial surface is covered with a thick layer of fibrin which is thrown into elevated areas and bands connecting the epicardial and parietal layers These shaggy projections of fibrinous exudate covering the entire heart give the typical bread and butter appearance of a cor villosum When the process is this extensive probably adhesions always are formed between the two pericardial layers At first these are fibrinous then the fibrinous exudate becomes the site of extensive granulation tissue which finally forms dense fibrous tissue The extent of these fibrous adhesions varies within wide limits Sometimes only a few bands are formed again areas several centimeters in diameter connect the epicardium and parietal layer and leave large parts of the pericardial cavity still potentially patent In others the whole pericardial cavity may be obliterated with fibrous tissue This obviously is a serious mechanical handicap because much of the energy of myocardial contraction is expended in pulling against the surrounding tissues Sometimes the fibrous exudate is 4 to 8 mm in thickness and forms a dense cuirass over the entire heart which cannot subsequently hypertrophy because of the confining covering

Peritoneum — Focal rheumatic peritonitis is found not infrequently post mortem when carefully sought Various types of lesions from fibrinoid infiltration of the hepatic capsule to fairly typical granulomata have been found in the peritoneal covering of the liver (Klinge 1933) and Paul (1930 b) has described typical rheumatic vasculitis in a liver close to the site of perihepatitis The foci of perisplenitis are less characteristic and often show areas of lymphocytes in nonspecific granulation tissue Local plastic peritonitis has also been described in cases of appendicitis

cytoplasm and are separated by strands of newly formed collagen Scattered through lesions of this age are varying numbers of lymphocytes at times plasma cells are found The area becomes less vascular and the remaining vessels show thick layers of media with flatter lining endothelium More and more collagen is laid down between elongated spindle shaped fibroblasts which seem to have evolved from the previously basophilic polyhedral cells Finally the area is made up of fibroblasts widely separated by dense collagen Sometimes nodules are found in which foci representing different stages of reaction lie close together This appearance probably is due to repeated rheumatic insults to the tissues which are especially vulnerable for it must be recalled that these rheumatic granulomata are prone to appear in tissues subjected to external or physiological trauma

Serous Membranes

Rheumatic involvement of the serous cavities practically always is accompanied by lesions of the underlying viscera In the case of the pleura and pericardium extensive exudates often are formed while in peritonitis the exudative process is more limited

Pleura — Pleural exudate on removal is fluid turbid and sometimes blood tinged but never frankly purulent It quickly coagulates on standing the fibrin clot settles to the bottom of the container and squeezes out a clear amber colored serum The total number of cells varies between one and fifteen thousand with a higher proportion of polymorphonuclears early and more lymphocytes later McEwen (1935) found from 7 to 74 per cent clasmatocytes and undifferentiated young connective tissue cells up to 7 per cent A most striking finding was the presence of desquamated mesothelial cells in every sample in proportion varying between 2 and 14 per cent These cells occurred either singly or in groups of two to four

From clinical roentgenographic and post mortem evidence we may reconstruct the pathologic picture of pleurisy as follows There are focal areas of rheumatic injury in the subpleural tissues with inflammation spreading to the pleura a plastic exudate is thrown out with little if any free fluid at first This is the stage of dry pleurisy with much pain and the auscultatory evidence of a rub but there is little if any, evidence of fluid either clinically or in x ray films The process may be limited to a small area or be widespread Quickly fluid collects and by separating the inflamed pleuræ relieves the pain at this stage characteristic physical signs and roentgenograms are obtained With the absorption of

Microscopic lesions have been described also in the wall of the trachea and more rarely in the esophagus

The lymph nodes draining the pharynx often are enlarged and present a microscopic picture indicating chronic irritation Klinge (1933) observed fibrinoid swelling in the capsule and follicular reticulum In some cases the lymphatic involvement seems to be continuous from the neck into the mediastinum The question as to whether this has progressed from the tonsils downward or has been the result of infection of the entire respiratory tract and is secondary to lymphatic involvement from the trachea bronchi and lungs cannot be answered at present

Lungs

The question of specific rheumatic pneumonitis is a moot point both from the clinical and the pathological aspect Several difficulties present themselves in interpreting the tissue changes which doubtless occur Most rheumatic patients with pulmonary lesions have a simultaneous carditis with passive congestion of the lungs there may be pulmonary atelectasis from large accumulations of pleural exudate from an enlarged heart or from pressure on a bronchus there may be a secondary bronchopneumonia finally it is theoretically possible for specific rheumatic lesions to occur in the lung Moreover two or more of these conditions may occur simultaneously Klinge (1933) agrees with Coburn (1933) that the lesions found in early stages present the picture of a non specific inflammation in which focal hemorrhages are prominent features Naish (1928) Fraser (1930) and Gouley and Eiman (1932) on the other hand found lesions which were considered more specific Macroscopically the involved areas are dark red airless and on section present a slightly moist granular surface giving a condition designated splenization The solid appearance is not due to atelectasis but to a true inflammation which Gouley calls a perivascular pneumonia and which both Naish and Fraser agree is closely related to perivascular lesions There are areas of focal necrosis and perivascular hemorrhages which extend into the alveoli with an outpouring of a moderate number of polymorphonuclears There is then a proliferation of both interstitial and perivascular cells and at the same time a thickening of the alveolar lining cells which practically obliterate the lumina of the alveoli This proliferate resembles that found in rheumatic granulomata and the proliferative process combined with the vascular lesions and focal hemorrhages secondary to the vasculitis makes up the picture which proponents of a true rheumatic pneumonia consider characteristic As already mentioned the difficulties in obtainin

which were apparently rheumatic in origin The peritoneal covering of the diaphragm is also implicated when there is much involvement of the underlying structure

Diaphragm The diaphragm is more often the site of rheumatic lesions than was formerly appreciated probably because of its proximity to the pleuræ and pericardium from which the infectious process seems to spread by direct contiguity and in addition the extensive musculotendinous junction probably furnishes a favorable locus where the toxic agent sets up the typical lesions Klinge states that the granulomata in the diaphragm contain relatively fewer giant cells than are found in cardiac Aschoff bodies but that in other respects the lesions correspond

Upper Respiratory Tract

The tissues of the throat probably are more frequently involved than are those of any other single organ Because he found peculiar lesions early in the course of the disease Gräff (1930) designated the early changes as the primary infection and described pictures somewhat different from the later lesions Klinge on the other hand considered many of the lesions as typically rheumatic in nature Aside from evidence of non specific chronic inflammation the tonsils show no characteristic alteration but on the other hand in the capsule and neighboring pharyngeal muscles all stages from simple fibrinoid swelling of the connective tissue to characteristic granulomata have been found The eventual scarring may lead to obliteration of the capsule in patients with recurring attacks MacLachlan and Richey (1928) who were among the first to describe accurately the rheumatic nature of the peritonsillitis also recorded instances where cartilage or bone has been laid down in the scars Characteristic end me and periarteritis also occur and Holsti (1927) found endarteritis verrucosa to be present frequently in the region of chronically inflamed tonsils

The base of the tongue shows diffuse infiltration with polymorphonuclears and later of lymphocytes and also in the submucosa and muscularis various stages of fibrinoid swelling and granuloma formation The same is true for the tissues of the nasopharynx and larynx In fact the lymphoid tissue of Waldeyer s ring seems to offer special opportunity for the noxious agent to penetrate the underlying connective and muscular tissues in which there may be dozens to hundreds of typical granulomata at a single time Occasionally on the vocal cords the granulomata may reach several millimeters in diameter when they present a laryngoscopic picture resembling the macroscopic appearance of subcutaneous nodules

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The base of the tongue shows diffuse infiltration with polymorphonuclears and later of lymphocytes and also in the submucosa and muscularis various stages of fibrinoid swelling and granuloma formation. The same is true for the tissues of the nasopharynx and larynx. In fact, the lymphoid tissue of Waldeyer's ring seems to offer special opportunity for the noxious agent to penetrate the underlying connective and muscular tissues, in which there may be dozens to hundreds of typical granulomata at a single time. Occasionally on the vocal cords the granulomata may reach several millimeters in diameter, when they present a laryngoscopic picture resembling the macroscopic appearance of subcutaneous nodules.

also noted the frequent continuity of the process in this region with that in the mitral valve rings as well as in the auricular pericardium. Macroscopically there are grayish yellow thickenings of the endocardium sometimes limited to the regions just above the mitral valve and at other times characteristically spread as tigroid markings over much of the auricle. Occasionally the smooth endothelium is replaced by flat sheets of fibrin and in chronic cases there may be plaques of calcium. Gross directed attention to the progressive development of endocardial reduplications as the process becomes chronic. Microscopically the fibrinoid degeneration is characterized by long bands of eosinophilic staining collagen along which the proliferated granuloma cells are arranged in palisades. Nearer to the inner surface are many distorted cells with crescentic or elongated nuclei arranged perpendicularly to the endocardium. Less characteristic areas of edema and exudative cells are distributed through the contiguous tissues even to the pericardium while in the myocardium there may be many typical Aschoff bodies. Newly formed capillaries appear rapidly and in the normally situated blood vessels is found the usual picture of rheumatic vasculitis. In the subendothelial zone there appears a substance resembling embryonic mesenchyme in which numerous fibroblasts soon develop with their nuclei directed toward the surface. Doubtless the function of many of them is to form the elastica so prominently distributed through the scars which also contain variable amounts of nonstriated muscle. In cases with multiple recurrences several stages of the inflammatory process are in close apposition. Healing slowly follows the pattern already described with residual scars some increased vascularity of the subendocardial layer and often myocardial hypertrophy of the auricle. If pericarditis has been extensive there may be irregular strands of scar tissue extending from the adherent pericardial layers down to the endocardium. Incidentally it may be mentioned that a process very similar to that just described sometimes may be seen in the first portion of the aorta.

Valves —Within recent years the conception concerning the pathogenesis of cardiac valvular lesions in rheumatic fever have undergone radical changes. From the hypothesis that the process is initiated by the implantation of a particulate infectious agent on the surface of the valve at the site where verrucæ subsequently arise and whence the inflammation spreads through the valve the emphasis has now passed to primary involvement of the interior of the valve. There still is a difference of opinion concerning the rôle of valvular blood vessels in carrying the noxious agent to the valves. For example Wearn Bromer and Zschiesche (1936) feel that such vessels exist in normal valves while

an uncomplicated tissue response in the lung of rheumatic patients makes impossible at present a final judgment concerning a specific rheumatic pneumonitis

Heart

An understanding of the forms the rheumatic inflammation assumes and the type of tissue specially involved together with knowledge of the finer anatomy of the heart helps in explaining the evolution of rheumatic carditis Verrucous endocarditis was long the center of the pathologists interest then the Aschoff body and later the lesions in other areas were described With more attention to correlating the material available with the clinical manifestations it is now evident that the apparently unrelated pictures are well related parts of a definitely continuous process

Myocardium — Rheumatic myocarditis is characteristically illustrated in the Aschoff bodies which form about foci of injured collagen in the intermuscular fibrous trabeculae usually close to small blood vessels Areas of edema and exudation of wandering cells are early present in the tissues surrounding the focally injured collagen Within a week or two there appear the typical proliferative cells which assume various spatial arrangements described in detail by Gross and Friedberg (1934 a and b) with the whole Aschoff body usually in the form of a spindle The contiguous muscle fibres may be fragmented or undergo waxy degeneration and also be directly compressed by granulomata The physiological integrity of the myocardium may also be violated by ischemic processes following compression of the blood vessels by perivascular granulomata or by narrowed lumina due to vasculitis and finally the whole cardiac musculature doubtless is affected by the general toxic process In many cases the simultaneous operation of all of these factors undoubtedly explains the prominence of cardiac symptoms In others the process is more subtile due to a more limited and slower action of the toxic agent During the involutionary stage the Aschoff bodies contain many lymphocytes in addition to granuloma cells which appear to be passing over into fibroblasts and eventually the site is simply a minute scar

Endocardium — While isolated Aschoff bodies in various parts of the subendocardium had been long recognized it remained for MacCallum (1924) and Von Glahn (1926) to describe accurately the characteristic left auricular endocarditis and recently Gross (1935) reported that macroscopic lesions were present in 80 per cent and microscopic lesions in all of the left auricles of eighty seven rheumatic hearts carefully examined He

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of inflammatory cells edema fluid and many capillaries and if the process is of several months duration there are larger thick walled blood vessels In subjects dying early there may be diffuse edema of the entire valve and many wandering cells and fibrinoid infiltrative changes may be seen in the collagen and elastica Often eosinophilic hyaline foci are present in the superficial layers of the valve both at the lines of closure and elsewhere A little later the proliferative picture and vascularization are more marked Occasionally Aschoff bodies are seen in the valve rings but more often the proliferated cells in the leaflets are arranged in palisades or irregular groups In vascularized valves both exudative and proliferative alterations may have a perivascular distribution At the height of the disease verruca formation usually is marked The verrucae are composed of hyaline material which may be derived either from the valvular exudate or from elements arising from the blood stream The endothelial cells at the bases of the verrucae become hyperplastic Cross described in the subendothelial zone appearances like embryonic mesenchyme seen in auricular endocarditis The chordæ may show comparable alterations particularly near their attachments and verrucæ sometimes are seen on their surfaces

A healing tendency probably is first characterized by recession of the exudate and fibrinoid infiltrate and the appearance of numerous lymphocytes the large basophilic cells assume more and more the shape of fibroblasts and these together with fibroblasts which have arisen in the valves and embryonic like mesenchyme lay down successive layers of collagen and elastica Fibroblasts which have grown into the verrucæ form fibrous tissue and the denuded surfaces of these warty growths become covered with endothelium derived from the hyperplastic cells at their bases Where verrucæ on contiguous leaflets have fused there are first bridges of fibroblasts then organization of scar tissue that firmly cements the structures together this results eventually in valvular stenosis Fusion of contiguous chordæ tendinae may be brought about by a comparable process The new formed capillaries so prominent in the earlier stages apparently disappear but the walls of the larger new formed vessels show fibro elastification and nonstriated muscle fibres and thus become permanently a part of the scarred valve

Holsti (1928) found a higher proportion of interstitial inflammation than of verrucous endocarditis in patients dying accidentally and Gross and Friedberg (1936 a and b) noted inflammatory exudates in practically all of the valve rings and in many of the leaflets both in the right and left sides of the hearts of patients dying during active rheumatic fever but the distribution of verrucæ was similar to that long known most

Gross (1937) and his coworkers consider that valvular vascularization is evidence of previous inflammation An ever increasing body of data however indicates that there is a close relationship between rheumatic lesions in the following structures left auricle pericardial wedges contiguous to the fibrous annuli of the valves valve rings and valve leaflets Failure to examine all of these areas in continuous sections doubtless accounted in part for the earlier conceptions concerning the evolution of verrucous endocarditis and the value of this technique is specially illustrated in the work of Gross whose systematic study of the whole problem has made it apparent that the evidence advanced by Holsti (1928) de Vecchi (1932) and many others probably furnishes the correct interpretation of the process viz primary inflammation in the substance of the valve with secondary changes on the surface Some observers on the other hand Siegmund (1928) Leary (1932) consider that the first injury is endothelial and the former cites experiments in which the cardio vascular endothelium markedly altered by infection or immunization undergoes hyperplasia when bacteria introduced into the blood are taken up by these superficial cells Two areas of the valves are specially subject to physiological trauma the lines where the leaflets impinge and the valve rings where there is a hinge like motion of the leaflets on the fibrous annuli It is of interest that these are the areas involved most markedly in rheumatic valvulitis

Macroscopically most fatal cases show along the lines of closure of one or more of the valves fine gray or reddish gray verrucæ although in cases succumbing early the valvular surface may be intact If the patient has suffered from recurring rheumatic fever the valves usually are thick with scar tissue replacing the delicate pliable leaflets and blood vessels may be easily detected In the auriculo ventricular valves especially in the mitral the chordæ may be short and thick with widening near their insertions or actual fusion to their neighbors This together with various degrees of fusion of the cusps and thickening of the edge of the valve leaflets results in the characteristic funnel shaped valve of mitral stenosis The semilunar valves show similar thickening of the cusps with verrucæ along the free margins and in the commissures the verrucæ on the contiguous leaflets sometimes fuse In recurring cases this line of fusion may be replaced with fibrous adhesions and unequal scarring in the valve may lead to eversion or inversion of the edge

Microscopically the picture usually is mixed with evidence of previous attacks mingled with those of the fatal one In the valve rings often continuous with the pathological process in the contiguous auricle pericardium aorta and the rings of other valves there are usually exudates

both in the gross and histologically resembles the endocarditis found in the left auricle More frequently the disease is a peri and mesaortitis There are rheumatic granulomata in the adventitia and fan like infiltrations along the branches of the vasa vasorum with focal destruction of the elastica and muscularis of the media In the vasa vasorum may occur typical rheumatic inflammation such as is seen in small vessels elsewhere Winternitz (1937) lays much emphasis on the importance of disease of the vasa vasorum in the production of arteriosclerosis of the larger vessels and the rheumatic nature of the disease of these nutrient vessels requires more careful investigation In many subjects with previous history of rheumatic fever there are found in the mesaorta dense avascular scars which were doubtless sequential to earlier mesaortitis All coats of the pulmonary arteries are sometimes similarly involved in this disease (Gross 1935)

All types of rheumatic alterations have been described in the smaller blood vessels in various parts of the body In early fatal cases Coburn (1933) noted numerous petechial hemorrhages which he attributed to markedly increased permeability of the finer vessels The simplest change is swelling of the endothelium which may be separated from the basement membrane by fibrin like material or a substance resembling embryonic mesenchyme The internal elastica may be split or fragmented in more advanced cases the media shows areas of fibrinoid infiltration and in extreme instances the degenerative process extends to the adventitia and there is extravasation of erythrocytes into the perivascular tissues This is very likely to occur in the spongy tissue of the lung Edema and collections of wandering cells are found in the vessel wall and large mononuclear cells form about the degenerated collagen and elastica In some vessels the embryonic mesenchyme like exudate pushes the endothelial cells closer and closer together and in it are formed thin walled blood containing spaces which communicate with the main lumen of the vessel As this becomes organized there is a picture like an organized canalized thrombus

In other instances the injured intima is replaced either concentrically or excentrically with thick bands of elastica which permanently narrows the caliber of the vessel Again the main replacement may occur in the media which may be much thickened with dense hyaline collagen or with bands of new formed elastica and muscularis Scars are found also at times in the adventitia especially when there has been a panarteritis with perivascular hemorrhage Occasionally the periarterial changes are so marked that it is difficult to differentiate the process from true periarteritis nodosa

often on mitral valves then with decreasing frequency on aortic tricuspid and pulmonic valves respectively Because Aschoff bodies were found also more frequently on the left side they agree with the present authors in attributing the peculiar distribution of verrucous endocarditis to functional trauma either from repeated hitting of inflamed leaflets on one another or from eddies set up in the blood current in the sinuses at the bases of the valves Because these phenomena are more marked in the left heart where the mechanical strain is the more violent there is probably a causal relationship Another point is noteworthy the exudative phenomena and capillarization of valves may recede and leave little evidence of their existence beyond the presence of some abnormal vascularity or of changes comparable to those that occur with advancing age

Conduction System — Because of its close anatomical relationship to the bundle of His one zone neither myocardial nor valvular should be specially mentioned that of the interventricular fibrous septum The septal leaflet of the tricuspid valve arises from this membrane and as the tricuspid valve ring is so often inflamed in rheumatic hearts (Gross and Friedberg 1936 a) it is readily understandable how easily the auriculo ventricular conduction system is affected by the exudative process that spreads by continuity from the tricuspid valvulitis Gross and Fried (1936) found exudation much more prominent than proliferation in the peri conduction system tissue and this probably explains the usual temporary implication of the A–V conduction system

Blood Vessels

The cardiac arteries and veins show all of the signs of rheumatic involvement described in blood vessels elsewhere and possibly with greater relative frequency While this cardiac vasculitis is doubtless important during the acute stages of the disease the permanent alterations that are induced may be equally serious for these histological changes i e fibrosis elastification and arteriosclerosis are of somewhat the same nature as those that occur in normally aging blood vessels and because of their occurrence in the first or second decade of life the hands of time for that individual may be set forward twenty or thirty years

Rheumatic vascular disease visceral and peripheral also is present frequently To this subject von Glahn and Pappenheimer (1926) made extensive contributions which many other have confirmed and extended Klinge (1933) even contends that much arterio clerosis has its origin in rheumatic fever In the aorta there occurs a form of endarteritis that

Symptomatology

A historical résumé of what has been thought to constitute the picture of rheumatic fever is helpful in understanding the modern concept of the disease. Out of the rather vague group of joint affections which went under the name "rheumatism" from the sixteenth century on a distinct type of migratory polyarthritis gradually became recognized as an entity. With the discovery early in the nineteenth century that endocarditis and pericarditis frequently occurred in patients with this type of arthritis, the first step was taken from the view that rheumatic fever was uniquely a joint disease. By the end of that century chorea and subcutaneous nodules had been added definitely to the picture and Cheadle (1889) had written his extraordinarily comprehensive accounts of the disease in childhood in which he stressed the relationship to tonsillitis and discussed pleurisy and various skin manifestations. In 1904 Aschoff described the characteristic changes in the myocardium and since then Klotz (1912) and Von Glahn and Pappenheimer (1926) have added to the list wide spread lesions throughout the vascular tree. Finally Klinge (1933) has marshalled evidence that in rheumatic fever characteristic lesions may occur in mesenchymal tissue generally. Thus within a century the concept of rheumatic fever has broadened from that of a disease of the joints to the present view of a disease of protean manifestations involving structures throughout the body.

The symptoms may be divided into those that are the general manifestations of infection, such as fever, toxicity, anemia and leucocytosis, and those more intimately connected with the specific disease. Among the latter are the four most characteristic manifestations, carditis, arthritis, chorea and subcutaneous nodules, and a number of less typical manifestations including various skin lesions, pleuritis, pneumonitis, peritonitis, tonsillitis, epistaxis and others. These groups of symptoms, called by Cheadle "the rheumatic series," tend to manifest themselves in various degrees of prominence in the different decades of life. In the infant the disease seldom occurs, but when it does, carditis is apt to be present alone. In childhood carditis and other visceral manifestations, chorea, rashes and subcutaneous nodules are at their peak, and polyarthritis is important. The latter, however, reaches its greatest severity among young adults, in whom chorea is less common and carditis less apt to result in serious cardiac damage, especially if the first attack occurs in this period. Finally, in later adult life and old age chorea occurs but rarely, polyarthritis remains the chief manifestation but tends to run a more

Various pathologists have described comparable vascular lesions in the kidneys and because rheumatic granulomata have been found also in these organs have considered rheumatic fever as one of the causes of chronic nephritis

Holsti and his collaborators (1927) have described a special form of disease in the blood vessels draining the nasal pharyngeal and gastrointestinal mucosa of rheumatic subjects and other observers have seen similar lesions in other visceral vessels They call the condition endarteritis verrucosa which in its end stage is characterized by finger like masses of connective tissue which are attached to the vessel wall at their bases and project into the lumina These verrucae or polypi are covered with endothelium

From the foregoing descriptions of rheumatic vasculitis it appears that involvement of the vascular tree in this disease may be almost as important as that of the cardiac muscle and valves This emphasizes again the conception of the general in contrast to the limited nature of the infectious process

Central Nervous System

While there is clinical evidence of frequent brain involvement if chorea is accepted as a rheumatic disease opportunities for examining this organ are rare Because the brain contains such a relatively small amount of tissue derived from the mesoderm it might be expected to show lesions not so typical of rheumatic fever Winkelman and Eckel (1932) emphasized the importance of diffuse edema in five fatal cases with cerebral symptoms and also of endarteritis of the small blood vessels Klinge (1933) found all of the rheumatic changes in cerebral blood vessels that have been found in those of other viscera Because of this vascular involvement it is not surprising that petechial hemorrhages should occur occasionally

Greenfield and Wolfsohn (1922) directed attention to the similarity in the lesions of encephalitis lethargica and chorea and described the latter as a diffuse or disseminated encephalitis affecting chiefly the corpus striatum and also involving the cortex and the pia arachnoid Many thrombi in the small arteries were found by them We have been struck by the diffuseness of the inflammatory process in two brains we have examined If equally as severe changes occur in those patients who do not succumb, it is evident that permanent cerebral damage is not common for most patients recover without appreciable evidence of altered cerebral function

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chronic course and carditis although not infrequently it accompanies the arthritis seldom causes so great damage as earlier in life save in hearts injured in previous rheumatic attacks

In short the picture is so varied that one can scarcely speak of typical rheumatic fever without taking the age of the patient into account, and a physician trained chiefly in adult medicine is apt to be surprised at the nature of the disease in children, as is the pediatrician who encounters it in patients of middle age These different tendencies in the various age groups are summarized in Table III

TABLE III

APPROXIMATE COMPARATIVE INCIDENCE OF VARIOUS RHEUMATIC MANIFESTATIONS IN DIFFERENT AGE GROUPS

Manifestation	Infancy	Childhood	Early Adult Life	Middle Age	Old Age
Carditis	++	++++	++	+	+
Subcutaneous Nodules	±	++	+*	–*	–
Chorea	+	+++	+	–	–
Erythema Marginatum	+	+++	++	+	–
Typical Polyarthritis	±	+++	++++	++	+
Atypical Persistent Arthritis	–	±	+	++	+
Growing Pains	±	++++	++	–	–
Other Vague Symptoms	+	++++	++	+	–

Patients in this age group with rheumatoid arthritis have similar nodules
** Chorea of pregnancy occurs in this group

Another difference in the age groups is the tendency towards explosiveness of the attacks in adults and towards vague onset in children Although in the adult the onset may be gradual it more frequently strikes rapidly and arthritis and visceral manifestations appear within a few weeks of each other In children conversely although the attack not infrequently starts abruptly the onset is more prone to be indefinite and

gradual and the various groups of symptoms of a single attack may make their appearance months apart

Furthermore in the child sooner or later the disease very frequently assumes a subacute or chronic form the little patient does not appear very sick but on the other hand he is never entirely well and does not grow and gain in weight as do normal children of the same age Not only are there symptoms due to involvement of the heart such as dyspnea on exertion and precordial pain but there is often the picture of chronic toxemia with low grade fever persistent emaciation anemia and an increased erythrocyte sedimentation rate Physical examination at times reveals signs of progressive cardiac damage again in others few signs can be found to account for the persistence of toxic symptoms

In all types of the disease there is a tendency for the manifestations to appear in cycles in children the different members of the rheumatic series may appear in succeeding cycles in adults the fever and arthritis often recur with each cycle less severe and extensive than the previous one although during the acute stage periodicity is often masked by the administration of antirheumatic drugs In addition to the cyclic character of the individual attacks the disease as a whole is recurrent in nature so that a patient once attacked not only has no immunity against recurrences but indeed has a high probability of having repeated attacks Another striking feature of rheumatic fever is the tendency for the same group of manifestations to appear during each attack in a given patient as though each individual has his own disease pattern (Roth 1937)

Prodromal Manifestations

In recent years much less has been said about the so called pre rheumatic state meaning the vague malaise poor appetite epistaxis enuresis pallor and other indefinite signs and symptoms not infrequently observed in children before frank rheumatic manifestations appear It seems highly probable that these symptoms indicate that rheumatic fever already exists in the patient and the authors agree with Findlay (1931) that there is nothing more nebulous in medicine than what is spoken of as the pre state of a disease

One prodromal event on the other hand is of utmost importance namely upper respiratory infections and especially tonsillitis As has already been discussed in the section on etiology there is often a silent period of one to three weeks duration following the tonsillitis nasopharyngitis or grippe when the patient seems well but at the end of this period the temperature again rises and rheumatic fever makes its ap-

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pearance The figures recorded by various observers for the incidence of preceding sore throat vary tremendously For example Pribram (1899) obtained a history of sore throat in less than 2 per cent of his patients while McCulloch and Irvine Jones (1929) record sore throat in 52 per cent of their series and some form of upper respiratory infection in 75 per cent

We have observed a definite history of sore throat before the attack of rheumatic fever or physical findings indicating tonsillitis or pharyngitis on admission to the hospital in approximately 50 to 60 per cent of our patients In a fair number of patients however the outstanding manifestations of the disease appear quickly following chilling of the body or exhausting exertion while in others no premonitory episodes can be recalled

The characteristic signs and symptoms vary so widely in extent and severity that they are best discussed under various headings

Fever

During an acute phase of rheumatic fever with or without polyarthritis the temperature ordinarily ranges between 102° and 104 F with diurnal swings of one to three degrees Temperatures of 105° or 106° are not rare however and conversely severe cardiac damage may occur in patients in whom the rectal temperature does not rise above 100° F As new joints are involved or visceral spread occurs there is a rise in temperature in the absence of spreading inflammation fever tends to fall The temperature chart is therefore a fairly accurate guide to the course of disease in most patients who are not under the influence of antirheumatic drugs if there is an increase or recurrence of the fever with no signs of involvement of new joints it is fairly safe to assume the onset or spread of visceral lesions For this reason it is useful for the physician to keep an accurate record of the arthritis as well as the usual fever chart The duration of fever varies within wide limits Very rarely abortive cases are seen without cardiac involvement in which the entire course is complete in two or three days In most cases however a period of high or moderate temperature is followed by many weeks or months of low grade fever which continues as long as active infection persists During this period the rectal temperature may be normal the greater part of the time with only occasional rises to 100° F at intervals of three to seven days Since a low grade fever of this type is one of the most important indications of persisting low grade infection usually carditis the necessity of taking temperatures rectally and continuing to do so systematically long into convalescence is obvious

Although fever is perhaps the most constant single evidence of rheumatic activity patients are seen occasionally who persistently have normal temperature in the face of other signs of activity This is especially true in chorea

A serious condition which fortunately is seen rarely today is rheumatic hyperpyrexia The temperature may reach 111° and the patient die after delirium and coma This type of fever usually does not respond to salicylates and appears to be due to encephalitis

Toxemia

Although this term cannot be used accurately in a disease in which the rôle of hypothetical toxins is unknown it serves as a convenient designation for certain of the clinical features during the acute phase of rheumatic fever such as the flushed face and bounding pulse sweating and mental dullness or irritability

In few diseases is sweating so marked a feature as in rheumatic fever during the acute phase Although present throughout the day it is most severe at night With the sharp fall in temperature following administration of antirheumatic drugs it may be of such drenching character that the bed clothes must be changed several times during the night This may induce maceration of skin unless special precautions are taken to prevent it A peculiar and characteristic sour odor has been attributed to the sweat in this disease but probably a similar odor would be noted in any condition associated with such profuse perspiration Besides general intoxication and antirheumatic drugs an additional cause of sweating in rheumatic fever undoubtedly is pain

How much the stupor and change in personality often noted in patients extremely ill with rheumatic fever is due to toxemia and how much to cerebral anoxemia secondary to cardiac failure is sometimes hard to decide However the existence of such symptoms in the absence of evident carditis and their striking improvement following administration of antirheumatic drugs in spite of persisting heart failure indicate that anoxemia is not always the cause

Pulse

The pulse rate in simple rheumatic polyarthritis tends to parallel the temperature curve but at a slightly lower level During the first week or two the pulse is full and bounding occasionally dicrotic With the modern use of antirheumatic drugs temperature and pulse usually are

pearance The figures recorded by various observers for the incidence of preceding sore throat vary tremendously For example Pribram (1899) obtained a history of sore throat in less than 2 per cent of his patients while McCulloch and Irvine Jones (1929) record sore throat in 52 per cent of their series and some form of upper respiratory infection in 75 per cent

We have observed a definite history of sore throat before the attack of rheumatic fever or physical findings indicating tonsillitis or pharyngitis on admission to the hospital in approximately 50 to 60 per cent of our patients In a fair number of patients however the outstanding manifestations of the disease appear quickly following chilling of the body or exhausting exertion while in others no premonitory episodes can be recalled

The characteristic signs and symptoms vary so widely in extent and severity that they are best discussed under various headings

Fever

During an acute phase of rheumatic fever with or without polyarthritis the temperature ordinarily ranges between 102° and 104° F with diurnal swings of one to three degrees Temperatures of 105° or 106° are not rare however and conversely severe cardiac damage may occur in patients in whom the rectal temperature does not rise above 100 F As new joints are involved or visceral spread occurs there is a rise in temperature in the absence of spreading inflammation fever tends to fall The temperature chart is therefore a fairly accurate guide to the course of disease in most patients who are not under the influence of antirheumatic drugs if there is an increase or recurrence of the fever with no signs of involvement of new joints it is fairly safe to assume the onset or spread of visceral lesions For this reason it is useful for the physician to keep an accurate record of the arthritis as well as the usual fever chart The duration of fever varies within wide limits Very rarely abortive cases are seen without cardiac involvement in which the entire course is complete in two or three days In most cases however a period of high or moderate temperature is followed by many weeks or months of low grade fever which continues as long as active infection persists During this period the rectal temperature may be normal the greater part of the time with only occasional rises to 100° F at intervals of three to seven days Since a low grade fever of this type is one of the most important indications of persisting low grade infection usually carditis the necessity of taking temperatures rectally and continuing to do so systematically long into convalescence is obvious

heart disease as a whole must be understood The latter may be subdivided into (a) active and (b) inactive rheumatic heart disease and of these the former is synonymous with carditis Thus the term includes active inflammation of myocardium valves endocardium and pericardium (myocarditis valvulitis endocarditis and pericarditis) occurring during rheumatic fever as distinguished from the purely mechanical damage to the various structures of the heart which comprises inactive rheumatic heart disease and which results from previous active inflammation The situation is analogous to that in infections of the palmar sheath of the hand during the active stage of such infections the hand is crippled because of the inflammation but crippling may still be present in the inactive stage years later because of scarring of the tendons with resulting mechanical inefficiency

In contrast to the known bacterial infections of the heart which as a rule inflict important anatomical damage only on a single cardiac structure (endocardium or pericardium) active rheumatic heart disease tends to involve all parts of the organ The non specific term carditis is useful in the description of cases of rheumatic fever with obvious heart involvement but in which the number of cardiac structures implicated is not clear Having made the diagnosis of carditis however the physician should endeavor by continued study of the patient from day to day to elicit evidence indicating more specifically which structures are bearing the brunt of the particular attack in question

While the earlier observers laid chief emphasis upon endocarditis today it is recognized that myocardial involvement is of greater importance in causing the heart to fail Striking proof of this is supplied by the numerous instances of children who have valvular defects and severe congestive failure during attacks of rheumatic carditis but whose cardiac reserve returns to normal when the active infection subsides in spite of persistently deformed valves Indeed it is almost axiomatic that hearts of young rheumatic subjects do not fail unless the myocardium is damaged so that such failure in rheumatic cardiac patients under 40 years of age is presumptive evidence of active infection and this probability is greater the younger the patient The other common signs of myocarditis are precordial pain and tenderness tachycardia out of proportion to fever electrocardiographic abnormalities and increase in the size of the heart Furthermore it is doubtful if rheumatic endocarditis or pericarditis ever occurs without accompanying myocarditis It is best therefore to consider that the myocardium has been damaged in all patients who show symptoms or signs of cardiac involvement

In recent years the term valvulitis has tended to replace endo

brought essentially to normal within a few days of the onset of arthritis and distinct increase in pulse rate a few days thereafter is highly significant of the onset of carditis Accompanying this tachycardia there is usually a return of fever even in the face of continued antirheumatic medication but the ratio between pulse and temperature is now reversed with tachycardia out of proportion to the degree of fever In addition to its role in indicating the onset or increase of cardiac involvement the pulse rate is a most useful index of the course of the disease and of the time when the patient may attempt to leave his bed However in a patient with rapid heart rate while apparently quiet it is advisable to record the rate while he is sleeping for a truer picture of the cardiac condition is often gained from the sleeping pulse rate than from the records made while he is conscious of medical examination or nursing attention Occasionally transient sinus bradycardia rather than tachycardia marks the early phases of carditis rates as low as forty per minute being present in spite of moderate fever and in the absence of atrioventricular block Abnormal rhythms such as varying degrees of heart block premature contractions and auricular flutter and fibrillation are discussed under *Carditis*

Respiration

An increase in the respiratory rate in proportion to the degree of pyrexia is seen in most patients Pulmonary manifestations such as pleurisy or pneumonia are accompanied by rapid respiration often with an expiratory grunt Rheumatic involvement of the myocardium and especially of the pericardium usually is attended by an increase in respiratory rate this being particularly true in children in whom rates of 60 to 80 per minute are not infrequent without detectable inflammation of the pleura or lungs Occasionally a patient will have a sudden rise in the respiratory rate due to great pain from arthritis following the application of analgesic measures or immobilization of the affected joints by pillows or pads this tachypnea quickly disappears Instances of this character are less frequently seen since the introduction of salicylates

Carditis

This manifestation of rheumatic fever is by all odds the most important not only from the standpoint of the initial general infection but especially so from that of permanent damage For an intelligent consideration of carditis the position it occupies in relation to rheumatic

ditis A sign (Ewart s sign) often present is an area of bronchial breathing and egophony at the inferior angle of the left scapula which is important because it is sometimes incorrectly interpreted as due to pneumonia This sign may also be caused by pleural effusion

When the organized fibrinous exudate causes extensive obliteration of the pericardial cavity and when inflammation has led to adhesions between the parietal pericardium mediastium and chest wall marked cardiac embarrassment and enlargement results from the continual pulling on the surrounding structures Occasionally on the other hand a thick fibrous pericardial sac develops so rapidly in children that it prevents the normal growth of the heart Such a patient would therefore suffer from severe cardiac insufficiency without any possibility of relief from hypertrophy of the cardiac muscle Fortunately some cases of pericarditis clear up without adhesions and without affecting permanently the efficiency of the heart

It has been mentioned already that rheumatic fever is more apt to lead to cardiac invalidism in the child than in the adult Not only is carditis a less common manifestation in older individuals but more important still it is far less prone to lead to permanent damage when it does occur Thus of seventy-eight patients under twelve years of age entering the New York University Division of Bellevue Hospital with their first attack of rheumatic fever 46 per cent had clinical evidence of carditis and 27 per cent had permanent cardiac damage following this first attack Of sixty seven similar patients over thirty years of age on the other hand 30 per cent gave evidence of transient carditis but only 7 per cent had signs of persisting cardiac damage on discharge (De Liee and McEwen 1938)

It has been commonly said in the past that the more severe the attack of rheumatic fever the more probable is severe cardiac crippling Probably this is true in cases starting with polyarthritis as the chief manifestation but it is now well known that advanced heart disease of the rheumatic type is common in patients whose rheumatic attacks were so slight as to have escaped notice This is well illustrated by the fact that in an adult cardiac clinic at Bellevue Hospital 19 per cent of patients with mitral stenosis gave no history of any rheumatic manifestation in spite of close questioning and in an additional 13 per cent the history disclosed merely vague symptoms which may or may not have been rheumatic in nature Doubtless many of these patients had had definite rheumatic fever during childhood which they later forgot but others must have had attacks of such ill defined character that their true nature was never realized

carditis is a designation for rheumatic inflammation of the cardiac valves. This has resulted from studies showing that the main and earliest lesions occur deep in the valve substance in contra distinction to those of bacterial endocarditis which are essentially endocardial. True endocarditis does occur in rheumatic fever however as part of valvulitis and also as mural endocarditis especially of the left auricle. The relative frequency of obvious involvement of the various valves is illustrated by the following figures reported by Von Glahn (1927) from a study of 109 necropsied cases: mitral 90.8 per cent, aortic 57.7 per cent, tricuspid 41.3 per cent and pulmonic 3.3 per cent. On the other hand active inflammatory lesions of the valve rings were encountered in a much higher proportion of rheumatic hearts by Gross and Friedberg (1936 a and b) and in the deeper portion of the valve cusps by Holsti (1928). Of the valvular defects encountered clinically, mitral insufficiency is the most frequent, mitral stenosis the most characteristic and a close second in frequency, while aortic insufficiency is third and aortic stenosis a poor fourth. The diagnosis of organic tricuspid and pulmonic valvular defects is difficult from physical signs and usually is made by inference, although careful histopathologic study indicates that tricuspid valvulitis is much more frequent than simple macroscopic examinations of these structures would indicate. While murmurs indicative of damage to the mitral or aortic valves usually persist after they have once appeared they not uncommonly disappear following the subsidence of active disease; such murmurs frequently return promptly with the next bout of rheumatic fever, suggesting that structures once attacked are particularly susceptible to reinfection.

Pericarditis was revealed in 37.5 per cent of Von Glahn's cases consisting of adults and children and 51.3 per cent of Findlay's (1931) made up of children. Gross and Fried (1936) found microscopic lesions in the pericardium in all of the active fatal cases and in about 80 per cent of the subjects who had several attacks of rheumatism. Although sometimes mild, pericarditis is a serious manifestation when severe because of the added element of danger during the acute phase and the possibility of adherent pericardium later. The precordial pain so common at the onset probably is due to the severe accompanying myocarditis which usually is present. The diagnosis is proven by the characteristic double shuffle friction rub by electrocardiographic signs or by rapid increase in the size of the heart with roentgenographic evidence of pericardial effusion. In this regard however it is to be stressed that it is sometimes impossible on x ray evidence alone to distinguish between pericardial effusion and marked cardiac dilatation secondary to myocar

fibrillation usually is permanent once it appears During the course of pericarditis alterations in the S-T segment similar to those occurring in myocardial infarction may be present these probably are secondary to inflammatory changes in the subepicardial layers of the myocardium

Since these abnormalities usually are present for only a few days the frequency with which they are encountered depends largely on the frequency with which tracings are made Unless electrocardiograms are taken almost daily normal findings are of little significance in excluding carditis abnormal tracings on the contrary always are highly significant

Arthritis

This manifestation for many years was considered the essential feature of rheumatic fever with heart involvement merely a complication Now however it has been assigned to its proper place and in the United States it appears to be relatively unimportant from the standpoint of permanent damage although of great concern to the patient during the acute phase of illness because of its associated pain

The typical attack of rheumatic polyarthritis in an adolescent or young adult is dramatic and severe Onset usually is fairly abrupt and often occurs one to three weeks following an upper respiratory infection One or several joints may be attacked initially and in these inflammation increases rapidly so that by the end of a few hours the attack may be fully developed Pain and tenderness are extreme swelling occurs and a pink mottling or diffuse redness of the skin appears over the joint In case not treated with antirheumatic drugs (Friedländer 1886 Graef and coworkers 1933) the inflammation is acute in a given joint for six to eight days and then subsides although some residual stiffness may remain two weeks or more However as inflammation subsides in one joint it appears in others migrating from one joint to another in this way until in severe untreated cases almost every joint of all extremities has been involved Even more striking than this tendency to migration in the arthritis of children and young adults is the response to adequate doses of antirheumatic drugs Within two hours pain may begin to lessen and after twelve hours the most severely inflamed joints may reveal merely slight residual tenderness with perhaps mild swelling and redness Before the introduction of these drugs it was not unusual to see each set of joints involved more than once giving rise to a polycyclic course of the disease Even today following the discontinuation of medication or after the diminution in the amount of the drug administered this polycyclic picture is seen frequently

Since the proper management of a patient with rheumatic heart disease depends on whether the infectious process is inactive or active the signs and symptoms of carditis are of sufficient importance to warrant repetition They may be divided into (1) conclusive and (2) presumptive signs Among the former may be listed (a) the appearance of a pericardial friction rub (b) the development of new diastolic murmurs (c) definite and rapid increase in the size of the heart and (d) the development of heart failure during an attack of rheumatic fever Among the presumptive signs of carditis should be included (a) gallop (b) precordial pain and tenderness (c) tachycardia out of proportion to fever (d) electrocardiographic changes especially prolongation of the atrio ventricular conduction time (e) the appearance of rheumatic subcutaneous nodules (f) the appearance of heart failure or auricular fibrillation even in the absence of other rheumatic manifestations in patients under 40 years of age who have physical signs of previous rheumatic heart disease (g) fever leucocytosis or increased erythrocyte sedimentation rate in rheumatic subjects in whom these findings cannot be accounted for otherwise and (h) the appearance of any rheumatic manifestation in a young person or in any patient who has previously suffered rheumatic cardiac damage In reading this list of presumptive signs of carditis it will have been noted that some such as the appearance of abnormally increased conduction time or precordial pain in patients with rheumatic polyarthritis are practically conclusive whereas others if considered alone would warrant little more than a suspicion In many cases the final judgment as to the presence or absence of carditis is extremely difficult to make and usually it is only by a summation of all the evidence that relative certainty is reached Obviously if in doubt it is best to assume the presence of carditis and treat accordingly

Electrocardiographic Changes — Sinus tachycardia and bradycardia have been considered under the discussion of the pulse Probably the most significant electrocardiographic change in rheumatic carditis is atrio ventricular block Most frequently this consists merely of an increased conduction time without dropped beats but all degrees up to complete block with idiopathic ventricular rhythm may occur Although 0 20 seconds is commonly accepted as the upper limit of normal for the P–R interval readings of less than this are significant in rheumatic fever if they represent distinct increases from the known normal of the particular patient in question Transient premature contractions are encountered commonly during phases of marked toxemia or severe carditis and less often, transient auricular flutter or fibrillation In patients with hearts severely damaged during previous rheumatic attacks auricular

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The appearance of a patient during the acute stages of an attack of rheumatic polyarthritis is very characteristic His face is flushed and often covered with beads of perspiration there is an expression of suffering and as the observer approaches the bed a look of anxiety lest the bed or patient be disturbed The fingers are separated and semi flexed the elbows flexed slightly and resting at the side of the body with the hands crossed over the trunk the knees are partially flexed and the feet partially extended The position between extreme extension and flexion assumed by most of the involved joints is the one of greatest comfort

By no means always however does the arthritis of rheumatic fever follow this characteristic pattern Frequently it is vague and the discomfort so mild that in children it is dismissed with the appellation growing pains The rheumatic significance of these mild pains in joint or muscles during childhood has been recognized fully during recent years so that it is perhaps well to point out that rheumatic fever is not the only cause of growing pains In adults especially past the age of thirty one or two joints alone may be involved severely and simulate gonococcal arthritis Also in the older age groups the proximal interphalangeal joints are more prone to be attacked and the arthritis is apt to persist over periods of weeks or months as low grade soreness and stiffness in spite of antirheumatic medication Thus in older persons the joint manifestation of rheumatic fever not infrequently takes on some of the features of rheumatoid arthritis

The swelling of rheumatic joints is due both to periarthritic edema and to effusion of fluid into the joint cavity As much as 40 to 50 c c of fluid may be aspirated from a single knee joint Cytologic studies of the fluid (McEwen 1935) have revealed no characteristic features and most investigators have been unsuccessful in isolating microorganisms from it Although the white cell count in the fluid may reach 40 000 per cu mm frank suppuration does not occur

The result of an attack of rheumatic polyarthritis almost invariably is complete return to normal The patient with rheumatic fever is in danger of becoming crippled by heart disease but not by that of the joints unless the condition pass over into a disease closely resembling rheumatoid arthritis a comparatively rare sequel in our experience but reported more frequently by European observers

Chorea

Sydenham s chorea stands unique as a manifestation of rheumatic fever in two respects (1) it may occur without fever leucocytes or in

creased erythrocyte sedimentation rate and (2) the lesions in the brain at necropsy do not follow the customary picture of rheumatic pathological changes Because of these differences and because of cases in which no cardiac damage ensues the rheumatic nature of chorea has been doubted by some observers especially neurologists who have explained the frequent association of chorea with rheumatic carditis arthritis and subcutaneous nodules merely as a tendency for two distinct diseases to occur together similar to the association for example of pneumococcus pneumonia and herpes labialis Nevertheless it is usually accepted that chorea is merely one manifestation of rheumatic fever and this belief has been strengthened by the knowledge that other manifestations may exist alone and that this monosymptomatic characteristic is not peculiar to chorea

The limitation of Sydenham s chorea to the period of childhood and adolescence is striking The peculiar purposeless and involuntary movements which characterize the disorder vary from the mildest twitching of a single extremity to contortions of such violence and extent that the patient cannot stand or sit and must be nursed carefully to prevent injury One or both sides of the body may be involved Facial grimacing is common and the severe involvement of the tongue may render coherent speech impossible Fine movements are impaired especially so that common tests in mild cases consist of having the patient unbutton his shirt or write his name The latter is particularly useful since the writings provide a permanent record of the progression and regression of the disease The movements disappear when the patient sleeps Children with chorea undergo personality changes and are more than normally emotional crying and laughing readily and often for no obvious reason Because of this and the facial grimaces these children sometimes are thought to be stupid at the onset of disease or are punished for misbehavior Very severe cases may pass through a paralytic phase during which muscles are so flaccid that the characteristic movements do not occur

The duration of individual attacks when untreated is from weeks to many months In cases of long duration and in repeated attacks often it is difficult to decide when the choreiform movements have ceased because the patient is apt to continue certain twitchings as a form of habit spasm Other rheumatic manifestations notably carditis may persist of course long after choreiform movements have subsided From such statistics as those of Jones and Bland (1935) and of Findlay (1931) it would appear that serious cardiac damage is less apt to occur in rheumatic patients with chorea than in those without it other observers however have found chorea less innocent

Subcutaneous Nodules

One of the most characteristic of all the lesions of rheumatic fever is the subcutaneous nodule They occur in 6 to 20 per cent of children with rheumatic fever (Merritt 1928) but are comparatively rare in adults with that disease although somewhat similar nodules occur in about 15 to 20 per cent of adults with rheumatoid arthritis (Dawson Sia and Boots 1930)

The nodules vary in size from a millimeter to a centimeter with wide variation in a single patient Pribram (1899) describes different sizes in different locations miliary in the tendons and tendon sheaths medium sized in broad tendons as they pass over joints and at their insertions large over bony surfaces lying close beneath the skin Still another rare type resembling a lipoma may occur in the subcutaneous tissues over the bellies of large muscles The nodules usually are not tender and seldom are accompanied by redness of the overlying skin If the skin is made taut the underlying nodules have a white appearance Sometimes they are more easily demonstrated by this maneuver than by palpation at other times they are found only after painstaking palpation Rarely they are attached to the skin With the exception of those located over bony surfaces such as the skull and patella usually they are freely movable often they are symmetrical in distribution and appear in crops Shortly after appearing usually they are diffuse and soft later more discrete and firm They disappear gradually after persisting for weeks or months Garrod (1890) gives the relative frequency of distribution in fifty patients as follows elbows hands knees ankles head shoulders hips scapular and clavicles

Nodules are found most often in children with severe carditis of a low grade but persistent type The patients show a prolonged course of mild or moderate fever with frequent relapses they do not seem able to overcome the infection but are anemic emaciated and never entirely well The clinical picture is more serious than can be explained on the basis of simple cardiac weakness persistent intoxication seems to be playing an important role At times there is accompanying chorea Because children with subcutaneous nodules usually suffer severe cardiac damage these lesions although harmless in themselves are of serious prognostic importance However the significance is not as immediately grave as was taught and we have followed for many years patients who once had subcutaneous nodules without subsequent evidence of the development of progressing cardiac disease

Cutaneous Manifestations

Of the various skin lesions which occur during the course of rheumatic fever none is pathognomonic However occurring in a patient known to have had rheumatic fever previously they are presumptive evidence of the return of active disease and even in a previously non rheumatic subject their presence suggests rheumatic fever as a possible causative factor

The commonest and most characteristic cutaneous manifestation is *erythema marginatum* These lesions which appear chiefly on the trunk neck and arms usually begin as small pink areas which may increase in circumference rapidly At the same time their centers regain a normal appearance leaving an irregularly marginate pink to dusky red outline somewhat resembling ringworm but without the scaliness of the latter The half or full circles thus formed measure one to two centimeters in diameter but contiguous lesions then coalesce to form ever widening rings Sometimes the advancing edges are slightly thickened so that they can be detected by light palpation There is no itching or other subjective symptom The entire evolution and involution of the lesion may require only a few hours but new ones usually are found over a period of several days and occasionally they continue to appear for months or even years They like other rheumatic skin manifestations except erythema nodosum are commonest in children and they occur usually in chronic low grade cases rather than in those that are more acute although they may occur in the latter type

Less commonly *urticaria* is seen and rarely *hemorrhagic lesions* appear The latter are unassociated with decrease in platelets and bleeding and coagulation time and capillary fragility are normal In considering hemorrhagic lesions which occur during rheumatic fever it is well to point out that non thrombocytopenic purpura is not necessarily rheumatic in origin even when it is accompanied by joint pain for the latter may be secondary and due to hemorrhages into the synovia Probably most cases of so called purpura rheumatica have nothing to do with rheumatic fever

Occasionally during rheumatic fever a few *petechiæ* are seen and occasionally they may be numerous In such cases bacterial endocarditis usually is suspected and can be excluded only by the clinical course and persistently negative results of blood cultures in poured agar plates

Erythema nodosum has been noted so frequently in rheumatic patients that some authors have considered it always rheumatic in nature whereas others encountering it in tuberculosis have designated it as exclusively

tuberculous Probably as has been stated by Collis (1932) erythema nodosum represents a change in tissue reactivity which may occur during the course of infection with a variety of microorganisms The appearance of typical red indurated lesions in rheumatic patients who react negatively to tuberculin is highly suggestive of their rheumatic etiology Moreover the induction of these lesions by injection of streptococcal extracts (Collis 1932) and the reappearance of new lesions in areas previously involved in patients so treated (Coburn and Moore 1936) is suggestive evidence concerning their etiology The deep seated tender indurated areas may occur in various sites but characteristically appear over the extensor surfaces of the arms and legs First a dusky red in color they then assume a deeper hue then take on a bruised appearance and slowly fade

Respiratory System

As mentioned in discussing etiology many attacks of rheumatic fever are preceded by definite infections usually of the upper respiratory tract Sore throat tonsillitis or pharyngitis is the preceding event most often mentioned by the patient but sinusitis and ordinary colds are frequent also Probably these episodes which occur one to four weeks before the attack of frank rheumatic fever are not themselves rheumatic manifestations but merely light the fuse which leads to the explosion On the other hand subacute inflammation of the throat tonsils and neighboring lymph nodes occurs also during the course of the disease and appears to be truly rheumatic at least in some instances Thus Graff (1930) and Klinge (1933) have described lesions in the tonsillar capsule and other structures of the throat which they consider histologically specific Indeed the former describes the pharyngeal lesion as the primary infection

Epistaxis is observed frequently in rheumatic fever especially in childhood In some patients it appears as an early sign in successive bouts of the disease so that the individual himself learns to recognize the approach of a frank attack It is seen in rheumatic fever of the low grade type as well as in the more acute form Although the cause is not definitely known it may result from vascular lesions of the type shown by Pappenheimer and von Glahn (1927) to occur in peripheral vessels or be due to the endarteritis verrucosa described by Holsti (1927) Indeed vascular fragility and minute hemorrhagic areas are seen frequently in other visceral areas

Laryngitis —Laryngitis may occur in three forms (1) a simple

catarrhal inflammation due to direct extension from inflammation in the pharynx probably not truly rheumatic in nature (2) rarely circumscribed nodules on the vocal cords (3) even more rarely acute edema of the larynx which may lead to respiratory obstruction An occasional cause of hoarseness during the course of rheumatic carditis is paralysis of the left recurrent laryngeal nerve from pressure by a greatly dilated left auricle

Pleuritis —Pleurisy has been detected clinically by different observers in from 2 to 20 per cent of cases of rheumatic fever it has occurred in about 10 per cent of our patients with the acute disease In fatal cases however it is probably more common for in twenty-eight necropsies Paul (1928) reported pathologic evidence of active pleurisy in 64 per cent The undoubted tendency for pleurisy to occur in patients with carditis and the greater incidence of pleurisy on the left side than on the right have been cited as evidence in favor of direct extension of the lesion from the inflamed pericardium On the other hand Paul reported a greater incidence on the right and four of his necropsied cases showed no pericarditis Thus the exact pathogenesis of the lesion remains in doubt

Ordinarily the rheumatic nature of this manifestation is obvious because it occurs most often one to three weeks following the onset of polyarthritis or is associated with definite carditis Occasionally however it is the first rheumatic manifestation to appear and in these cases its true significance is not appreciated until other evidence of this disease arises Cases of this second type have led to the conjecture that some instances of idiopathic pleuritis may be of rheumatic origin This probably is the case but in the present state of our knowledge it is probably better to assume that pleurisy is rheumatic in origin only when the latter disease becomes manifest in some other way

A typical attack is unmistakable Accompanying a rising temperature there is pain in the chest increased by deep respiration and cough and attended by shallow rapid breathing with splinting of the chest on the affected side Physical examination at this time reveals signs of simple dry pleurisy with fine crackling rales at the end of deep inspiration or a frank friction rub Within a day or two the physical signs change to those of pleural effusion at this time pain usually disappears An increase in the pleural exudate from day to day is at first shown only by physical examination or x ray but after a certain critical level is reached it is accompanied by increasing dyspnea Bronchial breathing and egophony are often present at the upper level of dullness and are sometimes erroneously interpreted as indicating pneumonia Thoracentesis seldom is necessary save as a diagnostic measure but if dyspnea becomes

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Laryngitis —Laryngitis may occur in three forms (1) a simple

lung often in the form of granulomata Paul (1928) on the other hand described acute hemorrhagic lobular pneumonia somewhat different in appearance from the usual type of secondary pneumonia He considered these lesions fairly characteristic though not absolutely specific in nature

Clinically a rather striking feature is the rapidity with which the signs of consolidation appear and recede Dullness altered fremitus bronchial breathing and numerous rales may be heard over a fairly wide area for a day or two then shift quickly to another lobe and be absent from the one first involved On the other hand only one area may appear to be implicated It is difficult to correlate the clinical evidence of acute exudation with the histopathological findings which are chiefly proliferative in nature and hence probably slow in evolution and involution Possibly the exudative features are similar in nature to the swelling and edema found about acutely inflamed joints and this may explain the evanescence of the signs

No account of pulmonary changes in rheumatic fever would be complete without a discussion of hemoptysis which is encountered so frequently among both inactive and active rheumatic subjects There can be little doubt that pulmonary hemorrhage in patients with inactive rheumatic heart disease is due predominately to the rupture of small vessels as a result of pulmonary engorgement secondary to mitral stenosis less frequently pulmonary infarction from either embolism or thrombosis is the cause In patients with active disease three additional possibilities exist namely rupture of a small vessel damaged by lesions of the type described by von Glahn and Pappenheimer (1926) rheumatic pneumonitis and capillary bleeding in the lungs comparable to purpura in the skin

Gastrointestinal System

Non specific gastrointestinal symptoms such as nausea vomiting constipation or diarrhea may occur during the course of rheumatic fever just as in other acute diseases and also may result from toxic doses of antirheumatic drugs Grenet (1925) Vining (1928) and others have suggested that the gastrointestinal tract may be the route through which the infectious agent gains entrance to the body in some instances a possibility which cannot be denied in the present state of knowledge although the supporting evidence is not convincing

A point of great interest in the gastrointestinal symptoms so frequently encountered is the nature of the processes which may give rise to them Rather characteristic abdominal pain occurs frequently in patients with this disease and not uncommonly it is the presenting symptom

troublesome it should be resorted to therapeutically True pleuritis with effusion occurring as an integral part of rheumatic fever must of course be differentiated from pleural transudation resulting from heart failure It must also be distinguished from non rheumatic pleurisies which may arise as complications the commonest causes of the latter are pulmonary infarction and bronchopneumonia

Aspirated fluid usually is amber in color and somewhat turbid and small flakes of fibrin often can be seen floating in it On standing a dense coagulum forms leaving a clear fluid Microscopic study reveals chiefly polymorphonuclear neutrophiles and degenerated mesothelial cells early in the course but later increasing numbers of clasmatocytes appear (McEwen 1935) Bacteriologic study by most investigators has failed to demonstrate bacteria

Signs of pleurisy persist from one to three weeks as a rule and then slowly disappear Usually some degree of pleural thickening and adhe sions remain and sometimes the pleural space is entirely obliterated A really thickened hyalinized pleurisy does not however result Patients who once have pleurisy as a manifestation of rheumatic fever, are apt to have it reappear with subsequent attacks

Pneumonic Lesions — Throughout the nineteenth century rheumatic pneumonia was a not infrequent diagnosis of French and English phy sicians but with the great surge of interest in the heart in rheumatic fever at the close of that period pulmonary lesions tended to be for gotten Recently however there has been a reviving interest in this phase of the disease Von Glahn and Pappenheimer (1926) have dem onstrated widespread changes in the pulmonary arterioles and the pos sibility of a specific form of rheumatic pneumonia has been raised again by Rabinowitz (1926) Gouley and Eiman (1932) Naish (1928) Fraser (1930) Coburn (1933) and others The clinical diagnosis of intrapul monary lesions during the course of rheumatic fever is difficult because passive congestion pulmonary infarction compression from pleural and pericardial exudates and from much dilated hearts massive collapse and secondary infection all cloud the picture A striking difference in opinion concerning the incidence of rheumatic pneumonitis is found in reports of various authors some believing it non existent while Coburn (1931) made the diagnosis in eleven of one hundred and sixty two patients That there are definite histopathologic reactions in the lung somewhat resembling the lesions present in other parts of the body seems evident from the records of the observers above mentioned Collections of proliferative cells some multinuclear which appear to be both mesen chymal and alveolar lining in origin are found scattered through the

lung often in the form of granulomata. Paul (1928), on the other hand, described acute hemorrhagic lobular pneumonia somewhat different in appearance from the usual type of secondary pneumonia. He considered these lesions fairly characteristic though not absolutely specific in nature.

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especially in children Such patients often are thought to have acute intra abdominal surgical conditions with appendicitis most frequently suspected In Coburn s (1931) series of one hundred and sixty two patients 20 per cent had acute abdominal pain without cardiac failure or enlargement of the liver Giraldi (1930) has divided his cases into three groups those with vague pain and other symptoms of gastrointestinal disturbance those with symptoms suggesting appendicitis and those presenting a picture of diffuse peritonitis The underlying pathological changes are known only imperfectly In those operated upon nothing may be found or there may be slight increase in serous peritoneal fluid with perhaps fibrin flakes slight injection of the appendiceal region or hemorrhagic enlargement of the mesenteric lymph nodes At necropsy perihepatitis and perisplenitis (Paul 1930 b) have been found as well as lesions resembling Aschoff bodies in the diaphragm (Klinge 1933) We also have seen somewhat similar lesions in the muscularis of the small intestine and Holsti (1927) and von Glahn and Pappenheimer (1926) have described various lesions in the smaller intestinal blood vessels Thus in addition to pain due to passive congestion of the liver or to mesenteric thrombosis and pain referred to the abdomen from inflammation of the heart or of a hip there are several theoretically possible causes which must be borne in mind namely specific rheumatic peritonitis granulomata or arteritis in the intestines mesenteric lymphadenitis and purpura with subperitoneal hemorrhages With reference to the latter however there is little to support the common assumption that most cases of Henoch s purpura are rheumatic in nature

The importance of correct diagnosis in rheumatic patients with abdominal pain is obvious Usually pain and tenderness are more diffuse than in ordinary surgical appendicitis and sometimes there is dramatic relief following the administration of antirheumatic drugs There is however no certain rule for distinguishing between abdominal pain of rheumatic origin and that requiring surgical intervention In doubtful cases there should be no hesitation about operating for the latter seldom causes serious harm if done unnecessarily whereas failure to operate might be fatal in the case of surgical appendicitis

Liver

The occurrence of perihepatitis has been mentioned Poynton and Schlesinger (1931) have described hepatic lesions similar to those in acute yellow atrophy and Chadwick (1928) Brown (1929) and others have reported minor deviations from the normal in liver function tests

not associated with heart failure Whether these are significant of damage greater than may occur in any acute febrile disease can be stated only after further study Long standing passive congestion may cause sufficient periportal fibrosis to result in so called cardiac cirrhosis this of course is a manifestation of heart failure rather than of rheumatic fever

Kidneys

Renal involvement of several types may occur in rheumatic fever It has long been known that slight or moderate proteinuria may occur during periods of fever just as in other febrile diseases In addition Goldring and Wyckoff (1930) have shown that associated with this proteinuria there is frequently a distinct microscopic hematuria as well as increase in the number of white blood and epithelial cells and casts they believe these findings are indicative of focal glomerulonephritis Goldring (1931 a and b) has described al o a rather constant increase in renal function as measured by the urea clearance test during the acute febrile stage of rheumatic fever and a transient decrease during convalescence These findings are interpreted as indicating renal hyperfunction during the height of the disease as a response to increased protein catabolism and renal hypofunction later due to toxic injury to the kidney parenchyma Blaisdell (1934) studied necropsies of sixteen rheumatic patients and found a perivascular inflammatory reaction of acute non suppurative type affecting the smaller arteries and arterioles in eight cases In four others perivascular scarring was present Glomerular damage of marked degree was found only once Goldring (1931) Coburn (1933) Loeb (1931) and others have reported examples of typical acute diffuse glomerulonephritis in patients with active rheumatic fever but this is not common Indeed in view of the frequency with which both these diseases follow hemolytic streptococcal throat infections the rarity with which the two occur in the same patient is striking

The damaging effect upon the kidney of certain of the antirheumatic dru s must be borne in mind and patients receiving them must be carefully watched for signs of renal irritation Derivatives of both salicylic and phenylcinchoninic acid may cause these changes (Boots and Miller 1924) but they have not been observed in our patients receiving ordinary antirheumatic doses of aminopyrine Another effect of these drugs is to cause green coloration with Benedict s solution so that patients sometimes are erroneously thought to have diabetes Due to water loss from fever and sweating the urine of acutely ill rheumatic subjects is apt to be concentrated and hence of high specific gravity

Miscellaneous Manifestations

Iritis — Iritis is a rare event in rheumatic fever Once it appears it is apt to recur with each subsequent attack It does not respond to antirheumatic medication but clears in the course of a few weeks without leaving permanent damage In this it differs from the iritis of rheumatoid arthritis which sometimes leads to progressive loss of vision

Orchitis — Orchitis is encountered extremely rarely and has never been observed in any of the authors patients Whether it is a true manifestation of rheumatic fever or merely a complication is not known It runs a mild course as a rule and clears spontaneously

Hematological Findings

Anemia — Anemia of the microcytic hypochromic (secondary) type is an important feature of rheumatic fever In acutely ill patients the erythrocytes and hemoglobin may fall rapidly in chronic cases especially in children with low grade but severe persistent carditis the fall is less rapid but is progressive unless checked Erythrocyte counts of two million or less and hemoglobin levels of 6 to 8 grams are not uncommon Anemia is mentioned often as an important diagnostic point to differentiate subacute bacterial endocarditis from rheumatic carditis and in large series of cases it is true that the former show the lower average readings In bacterial endocarditis the anemia is less in the beginning and becomes progressively worse while in rheumatic fever it is liable to be most intense early in the attack and tend to improve with appropriate treatment Other differential features are more important Rarely is transfusion necessary in rheumatic fever

Leucocyte Count — The leucocyte count is an important sign of rheumatic activity (Swift Miller and Boots 1924) During the acute phase of the disease counts of 12 000 to 20 000 are usual and figures of 30 000 to 40 000 not uncommon the predominant cell is the polymorphonuclear neutrophile As the temperature falls either spontaneously or in response to medication the white count drops rapidly toward normal but tends to be slightly elevated as long as active disease persists usually ranging from 9 000 to 12 000 The value of blood counts is increased if the proportion between young and older neutrophiles is determined Even with this refinement however the test cannot be relied upon alone as certain patients with unquestionably active disease persistently have normal counts

Erythrocyte Sedimentation Rate — In recent years determination of the

erythrocyte sedimentation rate has become the laboratory test of chief importance in deciding the course of rheumatic activity because it is a more sensitive index of this condition than is the leucocyte count and tends to give definitely abnormal readings in the stage of low grade rheumatic fever when the degree of leucocytosis often is equivocal Furthermore the weekly fluctuations are not so marked and it is not so much affected by the administration of antirheumatic drugs as is the leucocyte count Although numerous methods have been described the simple technique of Westergren is the one used most commonly However because marked anemia may give false impressions from simple sedimentation readings a technique such as that of Frnstenc (1930) or of Wintrobe (1935) which corrects for the diminished erythrocyte volume is preferable The relatively long column of blood in the Westergren method tends to overcome some of the errors introduced by anemia in the shorter tube procedures The sedimentation rate does not of course differentiate rheumatic fever from other infections but it is of great value in following the progress of the disease and in making the all important decision as to when active infection is past

Serological Findings

The various tests for determining the presence of antibodies against soluble products of hemolytic streptococci (antistreptolysins Todd 1932 a antifibrinolysins Tillett Edwards and Garner 1934) or against immunochemical substances obtained from the bodies of streptococci e g anti nucleoprotein precipitins (anti P) anticarbohydrate precipitins (anti C) or anti type specific precipitins (anti M) have served to show that hemolytic streptococcal infections often exist in patients with rheumatic fever These relationships have been discussed elsewhere Considered in connection with other data the presence of some of these antibodies at time helps in differentiating rheumatic fever from other diseases which have arthritic manifestations but let it be emphasized none of them has direct diagnostic import

DIAGNOSIS

General

In a disease with protean manifestations the need for a diagnostic test such as the Wassermann reaction in syphilis is obvious Unfortunately none is available in the case of rheumatic fever and diagnosis must depend upon the clinical picture presented by the patient

Two types of diagnostic problems are encountered commonly the first is presented by the patient with symptoms suggesting rheumatic fever in which case the physician must decide whether that is the correct diagnosis the second is found in the patient with a history of previous rheumatic fever and with clearly defined rheumatic valvular disease but with only vague evidence of active infection Here it must be determined whether the symptoms are due merely to the result of previous damage or to a combination of this condition and superimposed active rheumatic carditis This problem has been considered already in the discussion of carditis It should be emphasized however that the decision concerning such rheumatic activity is extremely important because upon this decision will rest the conduct of the case

Returning to the problem of the patient with possibly rheumatic symptoms clearly the ease and certainty of diagnosis will depend upon the character of the clinical picture The child with evanescent polyarthritis and high fever who develops a pericardial friction rub or subcutaneous nodules offers little diagnostic difficulty On the other hand it is very difficult to be certain about the underlying cause in a malnourished youngster who fails to grow gain weight and strength and who gives a history of repeated nose bleeds or vague joint pains and in whom a soft systolic murmur is heard over the precordium In considering the points in such a case it is very useful to document the various manifestations for let it be emphasized the picture is constantly changing and only by considering it at various phases can the correct diagnosis ultimately be reached The so called growing pains are very significant when they involve the upper extremities but less so when they are limited to the legs unless they are severe enough to waken the child at night Temperature curves sleeping pulse rates erythrocyte sedimentation rate estimations and curves constructed from these estimations low grade leucocytosis abnormal fatigability and cardiac signs tending to become more and more abnormal all are highly suggestive of active rheumatic fever The presence of erythema marginatum in doubtful cases has considerable diagnostic value and the finding of subcutaneous nodules will point clearly to the underlying cause in an ill defined picture such as that drawn above A high antistreptolysin titre or a rising curve has some suggestive value but cannot be considered determinative because it may exist in patients with simple hemolytic streptococcal infections

In adults the difficulty in atypical cases as a rule is that of distinguishing them from other diseases involving the joints The joints in rheumatic cases are more apt to show superficial pink marking and swelling of the type produced by intracapsular effusion although diffuse

pink to red edema is found often over the wrists and ankles Hard brawny indurations should warn the examiner to be on the look out for other etiologic factors The pain usually disappears promptly following adequate doses of antirheumatic drugs leaving no residual swelling or deformity but not infrequently in older persons it tends to remain in certain joints as a recurrent soreness sometimes for months

Differential Diagnosis

The diseases from which rheumatic fever must be differentiated are naturally those which give rise to symptoms or signs suggesting one or more of the rheumatic manifestations Most of these are di eases in volving the joints but there are a few which may simulate rheumatic fever in other ways notably bacterial endocarditis and hyperthyroid ism

Subacute Bacterial Endocarditis —The fact that this infection is often implanted upon valves previously damaged by rheumatic fever lends obvious difficulties for not only may the patient give a rheumatic history but the cardiac physical signs are apt to be characteristic of rheumatic heart disease Although joint pains may be present they differ from those of rheumatic fever in being seldom accompanied by objective manifestations other than localized pain or redness The petechiae sometimes seen in rheumatic fever are few in number and transient whereas in bacterial endocarditis usually there are constantly recurring crops of these lesions Similarly hematuria is more common in bacterial endocarditis and when present the red cells are more numerous than in the ordinary case of rheumatic fever Other dia nostic features indicating bacterial endocarditis are embolic phenomena and enlargement of the pleen Anemia is more striking and progressive in bacterial endo cardit s as a rule but a single red blood count is of little differential value in an individual case because rheumatic fever not infrequently is ac companied by marked anemia While electrocardiographic abnormalities are encountered more commonly in rheumatic carditis repeated records may be required to detect them and on the other hand a prolonged P–R interval may be found in a tracing from a patient with subacute bacterial endocarditis The temperature is more prone to be of septic type in bacterial endocarditis and the re ponse to antirheumatic drug less striking but these differences are not constant In recent years some doubt has been raised concerning the value of blood cultures in differenti ation between the two diseases because of reports of success in isolating non hemolytic streptococci from the blood of rheumatic patients Actu

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course has been followed over periods of months or even years Roentgenograms sometimes give useful differential information

Gonorrheal Arthritis — Contrary to the usual impression that this disease is monarthritic in nature the onset usually is characterized by a serous polyarthritis which may be easily mistaken for that of rheumatic fever On the other hand in most instances the polyarthritic phase is followed by a settling of the inflammation in one or two joints in which there is a brawny periarticular induration marked limitation of movement and little if any local response to the usual antirheumatic drugs even though the fever may be reduced temporarily When there is a recent history of gonococcal infection confirmed by the identification of gonococci in the discharge a useful diagnostic lead is presented but gonococcal arthritis often is encountered months and years after such infections and long after their symptoms and signs have disappeared The gonococcus complement fixation reaction is important especially when negative at the first bleeding but positive later in a recent study (McEwen Bunim and Alexander 1936) the test was positive at some stage in 98 per cent of cases of gonococcal arthritis The diagnosis is established beyond question when the gonococcus can be isolated from the joint punctate

Non Gonococcal Low Grade Pyogenic Arthritis — A relatively uncommon form of arthritis is one which clinically is similar to gonococcal arthritis but in which there is no direct or indirect evidence of gonococcal infection in the patient Bacteriological methods of differentiation are of no value in these cases unless the causative agent can be isolated from the synovial fluid but this type of arthritis usually can be easily distinguished from rheumatic fever by the brawny indurated appearance of the joints by the persistence of the local inflammation and by the lack of response to antirheumatic drugs

Acute Pyogenic Arthritis — Acute suppurative arthritis can be caused by infection with any pyogenic microorganism but the more common agents are pneumococci staphylococci and hemolytic streptococci certain cases of gonococcal arthritis also are of this type Those due to pneumococci are almost always closely associated with lobar pneumonia and the others are complications in generalized septicemia Usually only one or two joints are involved and the acute brawny induration the lack of response to antirheumatic drugs and the general condition of the patient make diagnosis simple Aspiration of the joint reveals frank pus from which the causative microorganism usually can be grown

Tuberculous Arthritis — This disease commonly is monarticular does not respond to antirheumatic drugs and is chronic Roentgenograms of the involved joint ultimately reveal destructive changes and decalcifica

ally however this is a rare finding and even when positive cultures are reported there is little difficulty for in bacterial endocarditis the micro organisms grow out in poured agar plates whereas in rheumatic fever even those who report the greatest success have been able to isolate streptococci only in broth cultures Furthermore the sera of patients with bacterial endocarditis agglutinate the non hemolytic streptococci recovered while those of rheumatic patients do not

Hyperthyroidism — Cases of hyperthyroidism without marked ocular signs or thyroid enlargement may be mistaken for rheumatic fever because of slight fever loss in weight tachycardia pounding heart action and a sound on auscultation which simulates a late diastolic murmur The correct diagnosis is made obvious by determination of the basal metabolic rate and the response to iodine therapy With this medication or following thyroidectomy the apparent diastolic murmur disappears

Rheumatoid (*Atrophic*) *Arthritis* — Well defined examples of rheumatic fever and rheumatoid arthritis are easily distinguished Typically rheumatic polyarthritis is acute in onset and associated with high fever response to antirheumatic drugs is dramatic cardiac involvement is common and characteristic deforming joint changes do not often occur the antistreptolysin titre is often abnormally high the sera of these patients as a rule do not agglutinate random hemolytic streptococci of Group A (McEwen Bunim and Alexander 1936) possibly a strain of a type homologous with that infecting the patient might be agglutinated In rheumatoid arthritis on the other hand the onset usually is gradual the temperature is very little elevated antirheumatic drugs are only moderately effective cardiac damage is rare permanent joint disability is the rule the antistreptolysin titre usually is normal and the serum agglutinates hemolytic streptococci belonging to several types of Group A However as has been emphasized by Dawson and Tyson (1936) there is considerable evidence that rheumatic fever and rheumatoid arthritis are closely related conditions and in some cases features of both diseases coexist Thus several of the authors patients with joint deformity of typical rheumatoid character have developed high fever and pericarditis and have shown at times high antistreptolysin titres and at other times positive agglutinins for hemolytic streptococci Furthermore regarding serologic tests it must be stated that in rheumatoid arthritis the anti streptolysin titre occasionally is high (Dawson and Olmstead 1936) and in typical rheumatic fever agglutinins for hemolytic streptococci occasionally can be demonstrated in low titre A careful search for type specific agglutinins has not been recorded In atypical cases it is sometimes impossible to decide between the two diseases until the patient s

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Syphilitic Arthritis – The tabetic arthropathy or Charcot s joint could not be confused with rheumatic polyarthritis but the latter may be simulated by syphilitic arthritis This disease involves one or several joints from which the treponema sometimes can be recovered It is usually a manifestation of congenital syphilis and hence appears chiefly in children The chronicity and other evidence of syphilis and mild signs of inflammation in spite of marked effusion help to make the diagnosis The arthritis clears under antiluetic treatment

Miscellaneous Infectious Diseases — Arthralgia or true arthritis has been described in all the following diseases anthrax cholera dengue diphtheria dysentery erysipelas glanders Haverhill fever influenza leprosy malaria measles meningitis mumps pertussis puerperal fever rat bite fever scarlet fever small pox typhoid fever typhus ulcerative colitis undulant fever and yaws Most of these may be dismissed without discussion but a few warrant brief comment

(a) Dysentery — About 3 per cent of cases of bacillary dysentery are accompanied by joint pain and swelling which usually appear after the disappearance of intestinal symptoms Diagnosis depends chiefly upon recognition of the underlying disease Response to antirheumatic drugs is incomplete The microorganisms have only rarely been isolated from the synovial exudate (Clifford 1926) Arthritis may also accompany amœbiasis In one patient with amœbiasis in the authors series there was joint involvement of a migratory character which responded dramatically to antirheumatic drugs It was impossible to be sure that the patient did not have amœbiasis and rheumatic fever concurrently, but no other manifestations of the latter disease appeared

(b) Haverhill fever (Place and Sutton 1932) — Although a rare disease this is of some importance in differential diagnosis because arthritis is a constant feature together with fever and rash Diagnosis can be established by isolation of the causative agent *Haverhillia multiformis* from the blood and by specific agglutination tests with the patient s serum (Parker and Hudson 1926 Scharles and Seastone 1934)

(c) Meningococcus infections — Arthritis is a fairly common complication in meningococcus meningitis occurring in about 10 per cent of patients Clinically it is similar to gonococcal arthritis

(d) Scarlet fever erysipelas and puerperal sepsis — During the bacteremic stage of these diseases acute suppurative arthritis may occur as a rare complication More common especially in scarlet fever and appearing in the third to the fifth week of disease is a form of polyarthritis similar to that of rheumatic fever Alone or with polyarthritis there may occur carditis of the rheumatic type It is highly probable that these cases are truly rheumatic in nature and that the preceding disease acts in the same way as does hemolytic streptococcal tonsillitis in starting off an attack of rheumatic fever after the customary latent period

(e) Ulcerative colitis — About 4 0 per cent of patients with this disease have joint involvement It is differentiated from rheumatic fever by the underlying disease and the chronicity of the arthritis

(f) Undulant fever — Undulant fever is accompanied by joint pain or by frank polyarthritis in about 50 per cent of cases This syndrome of joint involvement and persistent fever occasionally leads to an erroneous diagnosis of rheumatic fever The true nature of the disease is revealed by positive agglutination of various members of the Brucella group The causative agent sometimes can be cultivated from the joint exudate (Simpson 1930)

Osteomyelitis — Rheumatic fever may be suspected early in osteomyelitis but even at this stage the occurrence of chills and the limitation of inflammation to a single area often not truly arthritic in location should point to the correct diagnosis Later the possibility of rheumatic fever is excluded by the brawny character of the swelling and the lack of response to antirheumatic drugs Blood cultures should be made immediately in all suspected cases for staphylococci frequently are found in the blood stream

Gout — The acuteness of gout coupled with the history of previous attacks of joint pain which cleared without residual disability sometimes leads to a mistaken diagnosis of rheumatic fever However the suddenness of onset and the very acuteness of the inflammation point to gout and this is confirmed by the finding of a high blood uric acid content The presence of uric acid crystals in joint fluid sometimes is a useful diagnostic procedure In chronic gout or in patients with previous attacks the presence of tophi and of punched out areas in roentgenograms may be of great aid Certain of the antirheumatic drugs namely neocinchophen and amidopyrine affect both diseases favorably but pain and swelling in gout are little influenced by salicylates Colchicin on the other hand gives equally dramatic relief in acute gout but is ineffective in rheumatic fever

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Miscellaneous Infectious Diseases —Arthralgia or true arthritis has been described in all the following diseases anthrax cholera dengue diphtheria dysentery erysipelas glanders Haverhill fever influenza leprosy malaria measles meningitis mumps pertussis puerperal fever rat bite fever scarlet fever small pox typhoid fever typhus ulcerative colitis undulant fever and yaws Most of these may be dismissed without discussion but a few warrant brief comment

(a) Dysentery —About 3 per cent of cases of bacillary dysentery are accompanied by joint pain and swelling which usually appear after the disappearance of intestinal symptoms Diagnosis depends chiefly upon recognition of the underlying disease Response to antirheumatic drugs is incomplete The microorganisms have only rarely been isolated from the synovial exudate (Clifford 1926) Arthritis may also accompany amœbiasis In one patient with amœbiasis in the authors series there was joint involvement of a migratory character which responded dramatically to antirheumatic drugs It was impossible to be sure that the patient did not have amœbiasis and rheumatic fever concurrently but no other manifestations of the latter disease appeared

(b) Haverhill fever (Place and Sutton 1932) —Although a rare disease this is of some importance in differential diagnosis because arthritis is a constant feature together with fever and rash Diagnosis can be established by isolation of the causative agent *Haverhillia multiformis* from the blood and by specific agglutination tests with the patient s serum (Parker and Hudson 1926 Scharles and Seastone 1934)

(c) Meningococcus infections —Arthritis is a fairly common complication in meningococcus meningitis occurring in about 10 per cent of patients Clinically it is similar to gonococcal arthritis

Naturally the mortality rate in acute cases increases with the number of attacks the patients have undergone previously. Death during acute stages is rarer today than formerly because of therapeutic measures directed against the pyrexia and acute intoxication. Pericarditis increases the seriousness of the outlook, immediately because it denotes a marked pancarditis with the additional danger of sudden death from cardiac tamponade, and remotely because of the handicap imposed by an adherent pericardium. Steadily increasing cardiac dilatation with progressive signs of congestive failure, especially vomiting from splanchnic engorgement, is gravely significant. Subcutaneous nodules indicate a serious form of the disease. Occasionally they appear with acute severity and herald a fatal outcome, but usually they occur with the low grade, progressive type of disease in which the heart is severely damaged. Successive crops appearing over a period of several months therefore indicate very ineffective resistance on the part of the patient. On the other hand, patients with only one or two crops may recover with little permanent cardiac damage.

After puberty the probability of a first acute attack ending fatally is less than before, and this probability diminishes still more with advancing age. In a rheumatic patient of any age, however, failure to show definite improvement within a month or six weeks points to a limited capacity to develop the resistance so necessary for recovery. In this respect persistently rapid erythrocyte sedimentation rate and low grade leucocytosis are important indicators of continuing infection. On the other hand a steadily falling erythrocyte sedimentation curve, absence of leucocytosis and increasing body weight are favorable omens.

Ultimate Outcome

Recovery may be complete with no clinical evidence of residual damage to important organs, or there may be permanent damage to the heart.

In Continental Europe and Scandinavia a form of chronic arthritis is described which is thought to be due to rheumatic fever and is called secondary chronic arthritis. Edstrom (1935) reported that 11 per cent of his patients with rheumatic fever developed these chronic joint changes and that this tendency was much greater in subjects whose first attack of rheumatic fever occurred in the third decade or later. Whether these patients had the type of rheumatic fever usually seen in the United States is a moot point. In New York City Dawson and Tyson (1936) noted a higher incidence of mitral stenosis in patients with rheumatoid arthritis than in a control group with miscellaneous diseases and hence

that of rheumatic fever but the authors have seen several cases with such typical polyarthritis that it was impossible to be sure that the two diseases were not present simultaneously The diagnosis depends upon recognition of the underlying disease

Hemophilia As in the case of scurvy hemorrhage into the joints is accompanied by pain and swelling Again the diagnosis is dependent upon recognition of the underlying disease Antirheumatic drugs give only slight relief

Sickle Cell Anemia — Sickle cell anemia may simulate rheumatic fever The confusing symptoms are muscle and joint pain and tenderness and the occasional occurrence of periarticular swelling cardiac enlargement and murmurs secondary to the anemia further complicate the picture The diagnosis is made by the other features of the disease notably the characteristic changes occurring in the erythrocytes examined in moist preparations

Serum Sickness — Although the joint involvement frequently is somewhat similar to that of rheumatic fever the history of recent administration of serum usually makes the true nature of the process clear The arthritis of serum sickness is relieved by aminopyrine and less so by the other antirheumatic drugs but none has any effect upon the accompanying urticaria Serum arthritis is prone to involve the temporomandibular joint which is attacked very rarely in rheumatic fever

PROGNOSIS

Prognosis must be considered from two aspects that of the immediate attack and that of the ultimate outcome Of these the former is favorable as regards the patient s probability of surviving but relatively unfavorable as regards return to complete normality because of the likelihood of permanent cardiac damage When one considers also that a patient once the subject of rheumatic fever is prone to have repeated attacks each one of which is apt to add its component of cardiac damage it is easy to understand that the ultimate prognosis is more serious than the immediate and that the outlook in rheumatic fever is very different from that in lobar pneumonia for example in which prognosis is a matter essentially of the acute illness

The Immediate Attack

The mortality rates for acute attacks range between one and four per cent in patients whose hearts have not suffered serious damage previously

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suggested that some patients with rheumatic fever face eventual arthritic crippling. DeGraff and Lingg (1935) on the other hand found no example of chronic arthritis among 614 fatal cases of rheumatic heart disease. We have seen many instances of rather prolonged joint involvement with incomplete response to antirheumatic drugs in patients with rheumatic fever, especially in those over 30 years of age, but we have not as yet seen a patient with undoubted rheumatic fever develop deformity of the joints. Apparently rheumatic fever has a different influence in causing permanent arthritic damage in this country compared with Scandinavia, Germany and France, or else the criteria for diagnosis vary in the several countries. Whatever the explanation, chronic arthritic crippling is relatively unimportant in the prognosis of orthodox rheumatic fever as it is seen in the United States and Great Britain.

The most serious sequel of rheumatic fever is chronic cardiac disease and the ultimate prognosis depends upon the extent of the damage to the heart. The figures of various authors agree fairly closely concerning the incidence of such damage. Among 683 children with rheumatic fever followed by Findlay (1931) approximately 30 per cent either showed no evidence of heart involvement at any time or developed signs of heart disease which subsequently disappeared. Edstrom (1935), Coombs (1924) and Morse (1931) report figures of 20 per cent, 25 per cent and 37 per cent of complete recovery respectively. Edstrom, on the other hand, found permanent cardiac damage in only one half of his patients whose first attack of rheumatic fever occurred in the third and fourth decades of life and in only two fifths of those in whom the first attack occurred after forty. Even among children Findlay noted a comparable influence of advancing age. For example, among 32 whose first rheumatic attack occurred before the age of five years 47 per cent died within the first year and 97 per cent within ten years; among 57 with a first attack between 11 and 15 years of age the comparable mortalities were 24 per cent and 70 per cent respectively, while among 14 first infected in the first half of the third decade the mortality for the first year was 14 per cent and no more died within the subsequent ten year period. While these figures illustrate the influence of age linked factors on prognosis, the rates are higher than in this country. For example, Ash (1936) in an analysis of combined groups of 1770 children from Boston, New York and Philadelphia who acquired their rheumatic fever at an average age of seven and were observed over an average of seven years found cardiac involvement in 74 per cent and a death rate of 20 per cent.

The influence of sex is more controversial. Findlay estimated the death rate from cardiac sequelae to be ten times the normal expectancy

among rheumatic boys and twelve times among rheumatic girls compared with a corresponding ample of the normal population Cabot (1926) on the contrary reported the duration of life to be shorter in men than in women with rheumatic fever In the group studied by Friedberg and Tartakower (1931) and that submitted to careful statistical analysis by DeGraff and Lingg (1935) there was no difference between the two sexes as to life expectancy

The ultimate prognostic significance of the various rheumatic manifestations varies somewhat In patients with rheumatic polyserositis some degree of permanent cardiac damage is very probable the same is true in patients with subcutaneous nodules The final significance of murmurs appearing during an acute attack can not be determined until after several months observation for even though they indicate acute valvulitis it is possible for them to disappear completely with recovery from the active infection The prognostic significance of chorea is a moot point For example among Jones and Bland s (1935) patients only 3 per cent with chorea alone developed chronic cardiac disease compared with 73 per cent among choreic patients with additional rheumatic manifestations and 86 per cent among non choreic rheumatic children Over an average period of eight years death occurred in 0 7 per cent of the patients with pure chorea in 14 per cent of those with chorea and other rheumatic symptoms and in 32 per cent of the other rheumatic patients Ash (1936) found 13 3 per cent of children with chorea alone to develop valvular cardiac disease and 4 4 per cent fatal carditis compared with 70 per cent valvular disease and 25 5 per cent mortality among non choreic rheumatic children De Liee and McEwen (1938) studying the results of first attacks only noted an incidence of carditis of 10 per cent and of permanent cardiac damage of 6 per cent in children with simple chorea compared with corresponding figures of 46 per cent and 27 per cent respectively in children with arthritis Sutton and Dodge (1938) take a more serious outlook on chorea for over a period of six years or more 18 6 per cent of their patients with pure chorea developed permanent cardiac disease and when those with muscle and joint pains not true arthritis were included the figures reached 33 5 per cent Choreic patients with polyarthritis nodules or carditis had 72 8 per cent permanent cardiac damage at the end of the observation period compared with 71 9 per cent among non choreic rheumatic children Findlay (1931) who was obviously dealing with children of poor resistance noted a death rate among the various categories of initial manifestation as follows chorea alone 12 5 per cent chorea and arthritis 13 7 per cent arthritis 29 1 per cent carditis fol

lowed later by arthritis 42 8 per cent and carditis alone 66 6 per cent Whatever figures are taken it is obvious that chorea alone is the mildest of rheumatic manifestations and has the least serious prognostic implication of any of the rheumatic series but on the other hand it may have much more serious import than would be implied by the data of Jones and his coworkers or those of Coburn and Moore (1937)

The entire natural history of rheumatic carditis has not been followed extensively enough to give final prognostic figures If one takes his data from fatal cases alone as did DeGraff and Lingg (1935) a gloomy picture will be painted while the figures of Edstrom give a more cheerful outlook The former found that three fourths of 644 rheumatic cardiac patients who were followed until death had succumbed by the age of 40 The average patient had suffered his original attack of rheumatic fever at 17 showed signs of cardiac insufficiency at 28 had definite heart failure at 30 and died at 33 When auricular fibrillation appeared 34 per cent died within one year and 75 per cent within three years Among this group who had died the average patient had 11 years of economic usefulness and 16 years of life following his initial rheumatic attack On the other hand Edstrom s (1935) analysis of 694 rheumatic patients observed in Lund between 1911 and 1933 showed 9 2 per cent to have died from their rheumatic affection with an average duratio morbis of 14 years in the fatal group Twenty nine per cent had completely recovered 37 per cent were fully capable of earning their living in spite of signs of cardiac disease or arthritis This probably gives too rosy a hue to the picture for many of the patients had been observed for relatively short periods Among 155 of these patients who suffered their acute rheumatic attacks between 1911 and 1920 17 5 per cent had succumbed to their rheumatic affections by 1933 while among 338 first seen between 1921 and 1930 9 4 per cent were dead Thus the length of the observation period alters the mortality rate It is impossible to harmonize these two sets of figures for DeGraff and Lingg analyzed only cases of rheumatic heart disease that had terminated fatally while Edstrom s data covered all types of rheumatic fever both recovered and fatal The environmental and social factors in the two groups also were different Indeed data are as yet too small and not well enough analyzed in respect of the various factors that favor the onset and continuance of the rheumatic infection to permit current statistics to be applied specifically to any given case Our own experience indicates that there is a tendency towards recovery in most rheumatics and that when the infection is fully conquered a fair degree of valvular deformity can be well tolerated if the patient adjusts himself to his lowered capacity for work On the

other hand repeated recurrences or continued activity of the rheumatic infection lead to progressive cardiac damage and early death The prognosis in a given case must therefore take into consideration all of the favorable and unfavorable factors both in the individual and his environment for the algebraic sum of these factors will eventually decide the outcome

TREATMENT

For many years the treatment of rheumatic fever was concerned mainly with the relief of acute manifestations especially polyarthritis Today without minimizing the urgency of the acute phase it is realized that the care of the patient with subacute and chronic rheumatic fever is of equal or greater importance In this presentation these stages of the disease are considered separately following which various special therapeutic measures and the possibilities of prevention are discussed briefly

Treatment of the Acute Phase

General Care — Much can be accomplished for the patient acutely ill with rheumatic fever by intelligent management and good nursing although the modern antirheumatic drugs have made this part of the problem much simpler than it was formerly The patient should be guarded against direct drafts especially following severe sweating During the latter discomfort can be minimized by the use of wool or flannelette sheets and clothing The latter should be of a type easily put on and off so that the patient is disturbed as little as possible Frequent bathing followed by alcohol sponges and powder help to keep the skin in good condition but the number of baths given daily must be kept at a minimum during periods of severe arthritic pain

Diet — During high fever and pain patients will want little food and excepting fluids the intake should not be forced since with adequate treatment this phase is of short duration As soon as possible however every effort should be made to cater to the patient s appetite in order to avoid the wasting which accompanies a chronic disease Save in the presence of heart failure with visceral congestion and edema the diet may be as varied as the patient desires On more or less empirical grounds most physicians give an abundance of foods containing vitamins A and C Obviously both sufficient calories and adequate vitamins should be supplied At all times the patient should be encouraged to drink large quantities of fluids to make up for loss through sweating and to maintain elimination of waste products through the kidneys Because of the

general debility and long confinement in bed most patients require mild laxatives or enemata

Drug — The antirheumatic drugs which are discussed in greater detail on subsequent pages have a striking effect on the fever and arthritis and on the general toxicity of the disease Supporting medication such as cod liver oil and iron is less needed in the acute than in the subacute and chronic stages

Local Treatment of Arthritis — Formerly the local treatment of arthritis was important but today requires little comment because of the rapid relief of joint pain afforded by drugs Indeed relief can be induced so quickly that the elaborate local fomentations and wrappings previously employed would cause more pain during their application than their benefit would warrant Certain simple measures however are of great value during the period before drugs have taken effect The skillful arrangement of soft pillows will splint the joints in the most comfortable position of partial flexion and will also serve to support the weight of the bed clothes Especially helpful in the case of ankle or foot involvement is the lifting of the bedding from the feet by means of a firm pillow or other support at the foot of the bed

Antirheumatic Drugs — The so called antirheumatic drugs which include the salicylates cinchoninic acid derivatives and aminopyrine are the chief means of combating arthritis and fever and toxicity in this disease Not only is pain dramatically relieved but the other signs of local inflammation such as tenderness swelling redness and heat disappear, and fever and toxicity clear Beginning involvement in other joints regresses without running its natural course and no new joints are attacked Unfortunately however in spite of this therapeutic influence upon arthritis and fever which is as striking as any in the whole field of medicine the use of these drugs even in maximal doses has not the same spectacular effect on the most important manifestation, carditis A few dissenting opinions have been expressed Findlay (1931) believing that proper treatment with salicylate early in arthritis can prevent serious cardiac damage and Poynton and Schlesinger (1931) and Schlesinger (1930) reported that similar therapy following tonsillitis prevents subsequent rheumatic relapses These reports are not convincing however and the experience of investigators who have made well controlled studies (Graef and associates 1933 Lukens 1928) indicates that carditis and subsequent permanent cardiac damage occur just as frequently in patients placed on optimal doses early in the disease as in patients who did not receive them Indeed it is common to see subcutaneous nodules pericarditis or chorea appear for the first time in patients under the full

therapeutic effect of antirheumatic drugs Moreover considered from the broad viewpoint it is proper to inquire whether keeping the patient free from fever is an entirely rational procedure especially in the face of evidence concerning the benefit of fever therapy in chorea It is possible that the development of immune processes is accelerated by higher than normal body temperatures On the other hand the rapid heart action must exert a deleterious influence on that organ especially when it is the site of widespread inflammation Obviously an acutely congested and edematous valve leaflet will be more injured by pounding on its neighbor one hundred and twenty times a minute than eighty to ninety times Aside from this numerical factor if salicyl or aminopyrine exert the same antiphlogistic action in acute valvulitis as they do in rheumatic arthritis i e reduction of redness edema and exudative cells a trauma sparing effect would be expected Even in the presence of the available evidence that these drugs are not entirely curative the lot of the rheumatic patient would be hard indeed if he were deprived of them

Salicylates — The first drugs found to be of value in rheumatic fever were salicylic acid salycin sodium salicylate and methyl salicylate (oil of wintergreen) and later acetyl salicylic acid was added to the list The therapeutic effect being dependent upon the salicyl ion is governed by the proportion of this radical in the various members of the group Whereas it is of some value in the relief of pain and fever in a variety of diseases its action upon the arthritis of rheumatic fever is well nigh specific For maximal effect the amount used must be large and just short of the toxic dose Signs of toxicity are loss of appetite nausea vomiting tinnitus deafness visual disturbance and delirium If the drugs are continued beyond this point cyanosis and collapse occur Signs of renal irritation also may appear even with only moderate doses and there may be mild hematuria and cylindruria and even signs of renal insufficiency may appear Occasionally an acute psychosis is seen which may subside quickly or may persist for weeks Fairly commonly patients with idiosyncrasy to salicylates show various dermatoses which may simulate measles or scarlet fever Very rarely hypersensitivity to the drugs is so intense that minute doses induce collapse and even death Lest these accounts of the toxic side effects lead to the impression that the salicylates are dangerous drugs it should be emphasized that nausea and vomiting or tinnitus are the only untoward manifestations encountered commonly Hanzlik (1926) gives the mean toxic dose of sodium salicylate and acetyl salicylic acid as 11 to 13 grams (165 to 195 grains) for men and 9 to 10 grams (135 to 150 grains) for women the toxic dose of the latter drug usually is slightly less than that of the former

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Parker 1934) indicate that in susceptible individuals even small doses may lead to agranulocytosis For this reason patients receiving this drug should be under careful supervision From three to five doses of 0 3 gm (gr v) each may be given the first day according to the age and weight of the patient if nausea dizziness or abdominal pain occurs the drug should be stopped if no untoward symptoms arise and favorable therapeusis has not been attained the dose may be increased to a 2 0 to 2 5 gm total of (gr xxx to xxxviii) daily Because it is eliminated or destroyed rapidly in the body it is often well to distribute the total amount throughout the day between an early morning and a late evening dose As soon as arthritis is relieved the total dosage should be reduced gradually While aminopyrine is being taken a total white blood cell count should be made once or twice a week and if the number of leucocytes is 6 000 or less a differential count should be done to make certain that the granulocytes are not being reduced too greatly in number

In summary it may be said of the antirheumatic drugs that they are of equal effectiveness when given in therapeutic doses but that such doses are much smaller in the case of aminopyrine than in the others While these remedies are of the utmost benefit symptomatically they are not curative and their use increases the physician s responsibility to keep the patient at rest lest he be encouraged to attempt harmful exertion because of drug induced freedom from arthritic pain

Sulfanilamide — The hypothesis that hemolytic streptococcal infections are important etiologic factors in rheumatic fever leads directly to the idea that *sulfanilamide* might be an important therapeutic agent in this disease for its action in some definite hemolytic streptococcal diseases such as meningitis puerperal fever and erysipelas has been well demonstrated A recent investigation (Swift Moen and Hirst 1938) of this question indicates that this drug had a much greater toxic effect in patients with acute rheumatic fever than in most patients with other diseases accompanying this toxicity the rheumatic manifestations often were more marked It was therefore found impractical to give this drug in large doses such as are required for the cure of severe streptococcal infection and very little beneficial therapeutic action was observed in the patients who received the maximal amounts they could tolerate Whether sulfanilamide will have a prophylactic influence when given early to rheumatic subjects who have developed hemolytic streptococcal infections is a question not yet decided and one that will require careful clinical bacteriological and immunological observation of a large number of patients for its elucidation

The salicylates are best given in doses of 1 gm (gr xv) every hour for ten doses or until early signs of toxicity appear After the tolerated and therapeutic dose has been determined it should be continued a few days then gradually reduced a gram or two daily until it is stopped altogether If arthritis returns the drug should be increased or resumed for a few days and then another attempt be made to withdraw it In spite of Hanzlik's demonstration that salicylates can induce vomiting by a purely central action most physicians are convinced that these drugs are less apt to cause vomiting if given with equal amounts of sodium bicarbonate Findlay (1931) believes also that their efficacy is augmented by the sodium bicarbonate In patients who are vomiting from other causes it may be necessary to administer salicylates rectally In such instances 4 gm (gr lx) in 200 cc of warm water or starch solution may be slowly instilled two or three times daily until therapeutic effects are achieved Some authors have advocated intravenous administration but there seems to be no advantage to this method unless the patient is unable to retain salicylates given orally or rectally and cannot tolerate other drugs such as aminopyrine

Cinchoninic Acid Derivatives — Because of its usefulness in gout cinchophen was used early in the treatment of rheumatic polyarthritis and was found of benefit This drug was too often associated with gastric irritation to be of importance but its derivative neocinchophen has been used widely The effective dosage and signs of toxicity are almost identical with those of sodium salicylate but Boots and Miller (1924) found neocinchophen slightly less toxic and perhaps less effective than the latter Cinchophen should not be used because it may lead to acute hepatitis Neocinchophen is relatively safe in this regard although a few cases of hepatitis sometimes fatal have been reported following its use It is best given in the manner described for the salicylates

Aminopyrine — Schottmuller (1927) was the first to advocate this drug in the treatment of rheumatic fever Its therapeutic action appears similar to that of the salicylates and neocinchophen but it differs from them in being equally effective in much smaller doses and in acting much more quickly (Schultz 1931) Although occasionally accompanied by nausea or dizziness in our experience it is better tolerated than are the other antirheumatic drugs and it is especially useful in the presence of active carditis with resulting passive congestion of the digestive tract in that it is much easier to feed patients receiving aminopyrine than it is those taking aspirin or neocinchophen Therapeutic doses were thought to have no important untoward effects (Schultz 1931) recently however numerous reports (thorough review by Plum 1937 and Kracke and

Recent comparisons by Sutton and Dodge (1938) of choreic patients treated with fever therapy and untreated shows a reduction in recurrences of all of the members of the rheumatic series in the treated group when the patients were examined from one to six years following their acute attacks This was especially striking in the incidence of poly arthritis and in deaths from heart disease These authors are careful in their conclusions but if these results can be obtained in other series this form of treatment certainly will be indicated especially in those low grade types of rheumatic infection which run a chronic recurring course The abbreviation of the attacks of chorea make it distinctly valuable in this manifestation Attempts to apply it during the early stage of acute rheumatic fever should be very cautiously tried if it is essayed in this stage at all for a priori it is at this time that fatal hyperpyrexia might be most easily induced

Treatment of Miscellaneous Manifestations

Pleuritis —This manifestation does not respond to the antirheumatic drugs Pain is best controlled by strapping and codeine the former however often is not necessary and if used should be removed as soon as pleural effusion accumulates so as not to embarrass respiration Save for diagnostic purposes thoracentesis is indicated only when the amount of effusion is so great that it mechanically adds to respiratory distress Empyema is rarely if ever superimposed upon rheumatic pleuritis

Abdominal Manifestations —Since the treatment of abdominal manifestations due to rheumatic fever is symptomatic and not surgical it is highly essential to distinguish them from surgical conditions Because of the possibility of the latter laxatives should be used in patients with abdominal pain only with caution The diet should be light Probably depending on the nature of the underlying lesions some cases of abdominal pain of rheumatic origin are relieved by antirheumatic drugs while others are not An ice bag over the painful area sometimes gives comfort in other cases heat is beneficial In case of doubt concerning the nature of the complaint the safest course is to operate

Cutaneous Manifestations —As a rule these require no treatment but relief of itching occasionally is needed in urticaria Salicylates are commonly prescribed in the treatment of erythema nodosum but there is little evidence of beneficial effect The general care of the skin with daily bathing alcohol rubs and dusting powder is important as in other chronic diseases

Iritis —Iritis occurring during rheumatic fever clears spontaneously

Treatment of Chorea

Until recently the only treatment for chorea was prolonged rest in quiet surroundings sedatives and precautions lest violent movements cause injury Salicylates and arsenic had been advocated formerly but were found of no value Following 1919 favorable reports began to appear in the German literature concerning the use of nirvanol an phenyl enthylhydantoin which was later studied extensively in England (Poynton and Schlesinger 1931) It was soon observed that cessation of choreiform movements occurred only in patients undergoing a severe toxic reaction to the drug marked by rash and high fever and subsequent work indicates that this fever was the effective factor Since the use of the drug is associated with dangerous reactions and since fever can be much better induced by other means the use of nirvanol in the treatment of chorea is no longer justifiable

Fever Therapy — Because of marked improvement in a child with chorea following a febrile luminal reaction Sutton (1931) and Sutton and Dodge (1933) tried the effect of high temperatures induced in other ways She first used triple typhoid vaccine containing a total of 2 500 million bacilli in 1 c c intravenously starting with 0 05 to 0 1 c c and increasing the dose as needed to cause a daily temperature rise to 104°–106° F Depending upon the severity of the case from two to twenty treatments were required to stop the choreiform movements The efficacy of the procedure is shown by the fact that the average duration of chorea following the first injection was 8 5 days in one hundred and fifty children treated with typhoid vaccine as compared with 42 6 days in one hundred and fifty children treated with rest and sedatives alone Later (Sutton and Dodge 1936) radiant heat in an enclosed cabinet was substituted for the foreign protein injections with still better results The later method also has the great advantages that the degree and duration of fever can be controlled accurately and that only one or two treatment are needed Since Sutton introduced the principle various electrical methods of inducing fever have been tried by others in the treatment of chorea all with the same general result and the method is well established Because fever therapy contains an element of danger and may even lead to a fatal outcome the patient should be under the constant close supervision of the physician or a specially trained assistant during the entire seven or eight hours of treatment anyone contemplating this form of therapy should familiarize himself thoroughly with the technique before trying it

appeared beneficial in slowing rates above one hundred and forty even when due to sinus tachycardia Only carefully standardized preparations should be used the common standard is one cat unit to each 0 1 gm (gr 1ss) of powdered leaf A convenient method of administration is to give four cat units as the first dose followed in six hours by two units and then by two units morning and afternoon until a therapeutic effect is obtained or until the earliest signs of digitalis toxicity appear A maintenance dose of one or two cat units daily then is given as needed Care should be taken not to push the drug past the toxic point because vomiting once started may be difficult to stop especially in patients with severe visceral congestion

Treatment of Subacute and Chronic Rheumatic Fever

This phase of treatment although only briefly considered is equally as important as that of the acute stage Obviously from the nature of the disease the treatment of subacute and chronic rheumatic fever is for all practical purposes that of persisting low grade carditis Included in this phase are those patients convalescing from acute rheumatic mani festations and those with low grade carditis who have never experienced an acute episode

First in importance is prolonged rest in bed until all signs of infec tious activity have disappeared Certain requirements should be met before the patient is allowed to sit in a chair These are normal tem perature pulse and leucocyte count for a period of at least ten successive days in the absence of antirheumatic drugs satisfactory increase in weight good general appearance freedom from any rheumatic mani festation such as subcutaneous nodules or rash normal atrio-ventricular conduction time and a fall in the erythrocyte sedimentation rate to 10 or 15 mm per hour (Westergren method 1921) When this point has been reached the patient hould sit in a stationary chair a short time morning and afternoon the period is then increased about one half hour daily until the patient is up most of the day Short walks up and down the hospital ward then are begun and increased in extent and the patient finally climbs a flight of stairs before being sent home During this time the course of the patient is watched carefully and if there is evidence of reactivation of the rheumatic process exercise may have to be curtailed or discontinued temporarily The response of the heart rate to exertion is a useful guide for increasing or decreasing the exercise allowed The rate immediately before immediately after and five minutes later are recorded If the accelerated pulse found immediately after exertion re-

and does not lead to permanent damage as it sometimes does in rheumatoid arthritis Atropin to keep the pupil dilated cold compresses and protection from bright light usually are sufficient to give relief from pain

Epistaxis — This usually stops with rest and pressure against the bleeding point Occasionally it is persistent enough to play a part in the causation of anemia and in such cases the bleeding area should be cauterized

Treatment of Carditis

Rest — The measure of primary importance in the treatment of carditis is rest The enforcement of strict bed rest is easy during the acute phase of disease but as soon as the patient begins to feel better it usually becomes a major problem A C utch bed is very useful for treating patients with acute carditis even though orthopnea is absent however if such a bed is not available much can be accomplished by skillfully arranged pillows

Pain — Pain from carditis usually is dull but constant and limited to the precordium Occasionally it is sticking in character but even then it does not radiate Such pain is relieved best with codeine or more rarely morphine and an ice bag over the precordium antirheumatic drugs and amyl nitrite have no effect Another type of pain is encountered however in patients with aortic stenosis and insufficiency with or without active carditis which is paroxysmal severe and radiates to the arm and neck it is associated with sudden rise in blood pressure and is probably due to myocardial anoxemia from inadequate coronary filling This type is relieved by nitrites

Pericarditis — One feature of acute pericarditis requires treatment different from that of carditis in general namely the mechanical embarrassment which may result from a large effusion This is relieved by aspiration which especially in children is best done from the posterior approach (Sutton 1934) The usual indication for aspiration is respiratory distress and other evidence of circulatory insufficiency an indication for immediate aspiration is sudden fall in blood pressure suggesting as it does cardiac tamponade

Digitalis — The statement sometimes made that digitalis is contraindicated in active rheumatic carditis is in our opinion incorrect for we have found this drug to be an important remedy in both the acute and chronic stages of carditis The chief indications for its use are congestive heart failure and auricular fibrillation but sometimes it has

valescent sanatoria it must be admitted that no clear proof of the ultimate value of such treatment in rheumatic fever is at hand Indeed the results of one study (McCulloch and Irvine Jones 1929) seem to indicate that although children do well during convalescence they may lose a certain degree of resistance during the period of comparative isolation and as a result are more susceptible to recurrences on returning home *Obviously more data on this subject are required before final judgment* can be rendered but this type of therapy seems rational and valuable

Serum Treatment

Menzer (190_) was the first to advocate antisera in the treatment of rheumatic fever but this form of therapy was soon abandoned and Menzer himself later concluded that the beneficial results observed were probably due to foreign protein reactions In 19 7 Small revived the idea of specific therapy with an antiserum prepared against an indifferent streptococcus which he called the *Streptococcus cardioarthritidis* It was soon shown however that this microorganism bore no specific etiologic relationship to rheumatic fever and controlled studies (Hitchcock McEwen and Swift 1930) of Small s antiserum in rheumatic subjects showed it to have no specific value Coburn (1935 d) reported no benefit from antistreptococcal antitoxic serum

Vaccine Therapy — *On the theory that rheumatic fever may be due* in part to tissue hypersensitivity to streptococci (Swift Derick and Hitchcock 1928) and in view of the fact that in rabbits such hypersensitivity can be diminished by gradual intravenous immunization with these microorganisms Swift and his coworkers (Swift Hitchcock Derick and McEwen 1930) studied the intravenous use of streptococcal vaccines in rheumatic fever In the first few years of investigation beneficial results appeared to be obtained (Swift and Wilson 1931 Collis and Sheldon 1932) but subsequent observations concerning the prophylactic value of this form of treatment were disappointing (Wilson Josephi and Lang 1933) the treated subjects fared no better than controls From what we have learned subsequently concerning the numerous types of Group A streptococci which have infected rheumatic fever patients and which may possibly have been important etiological factors in their rheumatic diseases it is not surprising that the simple vaccines used by us failed in many cases for any theoretical immunity induced was very narrow in extent If and when vaccine therapy is attempted it should be guided by full knowledge of the immunological factors involved factors that are only beginning to be understood Our studies of patients

turns to the rate preceding that event it is safe to increase the exercise If on the other hand a rapid heart rate continues a more cautious attitude should be assumed and if this phenomenon is repeated for two or three days it may be wiser to return the patient to a regime of complete rest When marked slowing of a rapid pulse rate follows exercise one may assume that the exertion has a tonic effect The chief obstacle in carrying out this program is apt to be the patient himself who wishes to be up and about as soon as he loses the symptoms which induced hospitalization Insistence upon the importance of bed rest must be made with due regard for the urgency of the case and psychic attitude of each individual patient for the tactics necessary in one instance may lead to hypochondriasis in another

Some comments may be useful concerning the criteria of normal pulse and temperature The pulse especially in children may continue rapid when all other signs are satisfactory In such instances one usually finds that the sleeping pulse rate is normal and that the tachycardia observed during waking hours is due to nervous excitability rather than to carditis Occasionally a patient will continue to run a very low grade fever after all other criteria are favorable In such cases it is well to try the effect of gradually increasing time out of bed for occasionally the temperature may become normal on this regime

Coupled with rest certain measures such as good diet sunshine and fresh air are too obviously important to require comment Also iron or even small transfusions of blood may be needed to combat anemia and cod liver oil is useful as a general supportive measure

Treatment of Convalescence

The ordinary type of convalescent home is suitable for patients who have had bed rest until all evidence of active disease is past Unfortunately however most rheumatic patients sent to such institutions actually are still in the stage of low grade activity There is real need therefore for more sanatoria or hospitals such as those provided for tuberculous individuals where rheumatic patients past the acute stage of disease could be sent to recover full health in the best possible surroundings Such institutions are unnecessary in the case of the rich but rheumatic fever is a disease chiefly of the poor who must return to crowded and often unhygienic surroundings after discharge from general hospitals Provisions for this type of treatment are woefully lacking compared with those for combating tuberculosis although the two diseases are probably of comparable economic importance In urging the necessity for con

Careful statistical analysis of the ultimate effect of tonsillectomy in preventing relapses has given disappointing results. Wilson, Lingg and Croxford (1928) compared a group of two hundred and forty-seven children who had had tonsillectomy performed with one hundred and sixty-six who had not, and found that rheumatic manifestations occurred with approximately equal frequency in both groups; similar conclusions were reached by Hill (1928-29). Kaiser (1932), on the basis of observation on forty-eight thousand school children, concluded that tonsillectomy had little effect upon the incidence of rheumatic recurrences in children who had had previous rheumatic manifestations but that operation tended to prevent rheumatic fever in those who had not previously had that disease.

Unfortunately even less is known about the efficacy of removing abscessed teeth or of treating infected sinuses or other localized infections. It seems wiser, therefore, not to advise tonsillectomy or other surgical procedures directed against focal infection as routine procedures in rheumatic patients but to decide what should be done individually in each patient; this depends upon the importance of the focal infection in each case and the effect it may have upon the patient's general health. Since it is not certain that tonsillectomy is beneficial and since it may even be harmful in some instances, it seems better to resort to this operation only if the patient can be given adequate rest for several weeks after operation, during which period he can be watched carefully for recurrent rheumatic activity.

PREVENTION

Because of indefinite knowledge regarding etiological factors, measures directed toward the prevention of rheumatic fever are largely empirical but nevertheless some warrant discussion.

Infection. — Amidst many uncertainties the fact stands out clearly that hemolytic streptococcal infections of the upper respiratory tract are frequently precursors of rheumatic fever, especially in patients previously subject to that disease. It follows that every effort should be made to prevent exposure of rheumatic patients to these infections. In the home the patient or his parents must be warned against contact with other members of the family who may have colds or sore throats, and minute instructions should be given for the sterilization of dishes and other utensils used in common by the patient and others who have respiratory infections; measures to prevent droplet infection through the air should also be taught. In the hospital care must be taken lest rheumatic

in the subacute active stage of the disease did indicate that very small amounts of vaccine or streptococcal proteins could induce signs of rheumatic activity hence vaccine treatment if attempted must be carried out with care and with small slowly increasing doses

Climatotherapy

The well known rarity of rheumatic fever in the tropics led Coburn (1931) to transport a group of children with low grade active rheumatic fever from New York City to Puerto Rico Shortly after arrival signs of active disease began to disappear and the patients gradually improved Upon return to New York however relapses promptly appeared A more extensive study has been reported by Jones White Roche Perdue and Ryan (1937) in a group transported from Boston to Miami but with much less striking results from those described by Coburn From these comparatively small studies it appears that benefit may be obtained from a sojourn in tropical or subtropical climate but that these benefits may be temporary unless the patient remains permanently in that climate Indeed similar improvement is seen in most rheumatic children in the north when they have experienced several months of summer weather Whether it is connected with diminished exposure to streptococci or with increased resistance due to factors connected with fresh air and sunshine one cannot state Possibly it may be found that establishment of sanatoria for rheumatic patients under favorable climatic conditions will be as important as has been the case with tuberculosis While the latter have not entirely solved the tuberculosis problem they have been very important in prolonging useful lives of thousands of victim of that disease

Eradication of Focal Infection

The advisability of tonsillectomy in the treatment or prevention of rheumatic fever is argued repeatedly but unfortunately the answer remains in doubt Among those advocating tonsillectomy some (Robey and Finland 1930) believe that the operation should be performed early in the acute phase the majority on the other hand consider operating at this stage dangerous and advise waiting until the activity has subsided Certainly recrudescences of rheumatic activity occur frequently enough following tonsillectomy to suggest a relationship between operation and relapse Whether this relationship is due to bacteremia following tonsillectomy (Schwarz and Frisch 1929 Bartlett and Pratt 1931) is speculative

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patients be placed near to those with hemolytic streptococcal infections and attendants as well as visitors with colds and especially with hemolytic streptococcal infections should be excluded from the ward If a rheumatic patient contracts an upper respiratory infection he should be watched carefully during the next three or four weeks for signs of recurrent rheumatic activity and several estimations of the erythrocyte sedimentation rate should be made during this period A continued high rate or a recurring increase in rate after it had returned to or towards normal should be regarded as signs of rheumatic activity, and patients showing these phenomena should be watched carefully for other evidences of the disease Poynton and Schlesinger (1931) believe that the administration of sodium salicylate during this silent period may prevent rheumatic fever but other observers have not had such fortunate experiences

From Kaiser's data regarding *tonsillectomy* it would seem that this procedure might be useful in preventing rheumatic fever among those who have never had the disease but that it holds little promise for the prevention of recurrences in patients already attacked Indeed it is not the tonsils alone that harbor hemolytic streptococci, nor are these organs the exclusive sites in which these microorganisms induce disease of the upper respiratory tract Any portion of Waldeyer's lymphatic ring and the numerous lymph nodes draining this area may serve as nidi of chronic focal infection While therefore we believe that tonsillectomy should be performed in people who have suffered repeatedly from tonsillitis especially if there is a family history of rheumatic fever we also think that other portions of the upper respiratory tract likewise should be carefully observed for recurring or persistent infection Much work remains to be done even in the correct diagnosis of infection of this large and complex area

Climate — The reports of Coburn Jones and coworkers and others previously discussed suggest that individuals susceptible to rheumatic fever can avoid the disease by living in a tropical or subtropical climate For those who can afford it and who do not wish to make their permanent homes in the South it would seem of value to sojourn there at least during the late winter spring and early summer months when the incidence of rheumatic fever in the North is at its peak

General Hygiene — It is clear that all measures which raise the individual's general resistance must be of the greatest importance in preventing rheumatic fever Included in these measures are not only the obvious ones of good food rest and sunshine but also those which act indirectly such as adequate housing and other accompaniments of a high standard of living

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CHAPTER III

GONOCOCCIC INFECTIONS

By CHESTER S. KEEFER

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Introduction

It can be stated with confidence that gonococcic infection is preventable as well as curable It will be admitted generally that greater strides have been made in the treatment of established gonococcic infections in the last ten years than ever in the past Following the introduction of the sulfonamides and penicillin the total duration of gonococcic infections in both males and females has been reduced greatly and there is highly suggestive evidence that there are fewer cases of systemic infection with such complications as arthritis Gonococcic urethritis often can be cured within twenty four to forty-eight hours following treatment with penicillin and the same is true of gonococcic ophthalmia and gonococcic vulvovaginitis These brilliant and phenomenal results should encourage every physician to recognize infections early and to start treatment at once The importance of early and thorough treatment in all cases should be made a matter of common knowledge to both physicians and the lay public

The question of preventing gonorrhea is from the practical point of view an extremely complicated one It carries with it many problems in the socio-economic aspects of living and it involves many of the emotional and sex behavior problems in groups as well as in the community as a whole A vigorous attempt has been made by the United States Public Health Service the Army and Navy and the National Research Council in this country to define the various factors responsible for the spread of venereal disease and to attack the problem on many fronts in a realistic manner The reduction in the total number of cases can be accomplished only by cooperative efforts on the part of those responsible for the health and welfare of the people as well as by an enlightened public In this program the physician should play the leading role

In this article attention will be drawn in particular to those problems in gonococcic infection that are likely to come within the scope of internal medicine These include for the most part the secondary results of gonococcic infection due to invasion of the blood stream by the gonococcus from a primary focus of infection Since many cases of gonorrhea are now being treated by general practitioners and internists however it is well to review some of the features of local gonococcic infections as well No patient can be considered cured unless the local lesion has been sterilized and healing has taken place It is important then that all physicians should be familiar with the local as well as the systemic manifestations of this infection and they should be thoroughly conversant with modern techniques in diagnosis and treatment

Infection with the gonococcus usually originates with a local infection in the genital tract although in many systemic infections it may be difficult or impossible to determine the focus of entry This is especially striking in gonococcic arthritis of the newborn in boys In general however the infection involves the anterior urethra of the adult male and the genital passages of the female During infancy and early childhood ophthalmia neonatorum and vulvovaginitis are the commonest forms of infection Proctitis and stomatitis also have been described oftenest in infancy Rare cases of meningitis without a primary focus of entry have been observed in adults as well as in children It is plain therefore that one must be prepared to recognize gonococcic infection no matter where the focus of infection may be This is more important today than ever before because specific methods of treatment are now available and the earlier treatment is established the better will be the results

In Table I there are listed the various areas of the body that may be involved in gonococcic infections with an indication of the mode of extension of the infection

TABLE I

Local Infections			
	Urethra	Extension	Posterior urethra Prostate Seminal vesicles Epididymis
	Cervix uteri	directly	Salpingitis Oophoritis Pelvic peritonitis Subdiaphragmatic peritonitis
	Conjunctivae		Sclerae Ocular bulb
	Rectum Mouth		Ischiorectal tissues
Extension by blood stream		Common manifestations	Joints Tendon sheaths Endocardium Conjunctivae
		Less common	Bursae Bones Periosteum Muscles Perichondrium Skin Kidney Liver Pericardium Lungs Meninges Spinal cord

Local Gonococcic Infections

Urethritis

The diagnosis of gonococcic urethritis in the male is not difficult, since the symptoms of an acute urethritis usually occur within three to five days after sexual exposure and the discharge contains many gonococci, which can be detected by staining and culturing the exudate Every patient with a urethral discharge should have a careful examination of the exudate for gonococci for the reason that non gonococcic urethritis sometimes is encountered and requires entirely different management

In the vast majority of cases the infection is confined to the anterior urethra Every effort should be made to prevent it from spreading to the other structures of the genital tract One of the ways of doing this is early diagnosis and systemic treatment with penicillin All local treatment in the form of irrigations and the local application of chemicals should be avoided

When other parts of the genital tract become involved the services of an expert and skilled urologist are required It should be stressed however, that systemic treatment for gonococcic infections of the genitourinary tract is more important than local therapy In some cases combined treatment may be needed This decision should be reached by consultation with the urologist The lesions requiring special attention are posterior urethritis, prostatitis, seminal vesiculitis and epididymitis

In any patient with urethritis rest early treatment with penicillin and abstinence from alcohol coitus and sexual excitement are exceedingly important in the treatment

Treatment — The most effective treatment schedule for gonococcic urethritis is as follows 25 000 units of sodium or calcium penicillin every 3 hours for 6 doses given intramuscularly This should be followed by periodic cultures and smears for a period of 3 weeks before the patient is declared cured In some cases it may be well to administer sodium penicillin in capsules containing 25 000 units every 3 hours for 3 days after the initial intramuscular treatment All patients who are treated for gonorrhea should be given instructions concerning venereal prophylaxis

Vulvovaginitis in Children

This is a problem of the greatest importance to public health workers and to hospitals and schools but it is especially important for the patients who have the disease In view of the brilliant results reported by Sako Tilbury and Colley following a single injection of 100 000 units of penicillin prompt recognition of

the disease is essential because rapid cure can be obtained in a high percentage of cases following one injection of penicillin Fifteen out of 16 cases recovered promptly The only patient who failed to respond to the first course was cured by the second one

The diagnosis can be made with ease by culturing and studying the stained smears of exudate from the vagina and vulva of infected infants or children The discharge generally is profuse and there is an intense inflammation of the genitalia

The source of the infection in these cases is important since a discovery of the source of infection and its elimination will prevent other cases and the spread of the disease There are two common sources of infection infection of parents or nursemaids and sexual curiosity and experimentation Contaminated fomites such as rectal thermometers enema tips diapers towels and linen or an infected toilet seat may be important in some cases but intimate personal contact with an infected person is much more significant and this possibility should always be investigated It should be stressed that examination of sexual and other personal contacts is imperative since it has been shown that in at least 50 per cent of the persons who served as sources of infection the individual did not realize that he or she had an active gonococcic infection Information concerning infection obtained by interview alone is extremely unreliable

Treatment — The treatment in all cases of vulvovaginitis should be penicillin given systemically All contacts should be discovered and treated at the same time A single injection of 100 000 units intramuscularly followed by capsules each containing 20 000 units every 3 hours for 3 days should be given Cures should be controlled by means of bacteriological culture and a careful follow up examination for 3 weeks

Ophthalmia

This disease is most frequent in infants and is acquired from the mother at the time of birth In view of the fact that the infection may have serious consequences and cause the loss of vision every effort should be made to prevent it by treating every pregnant woman with gonorrhea with penicillin before delivery and by using prophylactic measures in the newborn

The conjunctivae should be examined every day following birth and if exudate is present or signs of inflammation appear smears and cultures should be made at once and if gonococci are found treatment started

Treatment — Penicillin is the drug of choice One hundred thousand units a day should be given intramuscularly in divided doses until all gonococci have disappeared and signs of acute inflammation are subsiding Penicillin in physiological salt solution containing 5 000 units per cubic centimeter may also be used locally All cases should be treated in consultation with an ophthalmologist

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gall bladder or pleurisy might be suffering from adhesions between the liver and abdominal wall complicating a pelvic infection due to gonococci It was 4 years later that Fitz Hugh clearly described 3 cases in which there seemed to be no doubt that acute gonococcic peritonitis of the right upper quadrant was present complicating a gonococcic infection of the pelvis Since then others have recognized similar cases Stanley has reviewed the description of 129 cases which have been reported

The clinical features and course of this syndrome have been well documented and may be summed up as follows The patient is usually a young woman between the ages of 20 and 35 years a period when gonorrhea is most prevalent Preceding gonococcic infection may have occurred as long as five years before the onset of the acute symptoms On occasion the peritonitis of the upper quadrants may have its onset concomitantly with other signs of a pelvic peritonitis or it may dominate the clinical picture so that the pelvic peritonitis is not a prominent feature The initial gonococcic infection may have been overlooked due to its latency Direct questioning may disclose a history of menorrhagia or dysmenorrhea burning on urination vaginal discharge or pain in the lower part of the abdomen a few days or weeks preceding the onset of symptoms of peritonitis

The onset of the disorder is punctuated by an acute attack of pain in the upper part of the abdomen which soon localizes in the right or left upper quadrant It is more common on the right side but it may be left sided or bilateral at the onset and it may affect alternately one side and then the other The pain is severe and is localized beneath the surface It is most intense anteriorly beneath the costal margin but it may be referred to the shoulder the lumbar or costovertebral area or over the lateral part of the chest wall In brief the pain is referred to those sensory segments which innervate the diaphragm The pain is greatly aggravated by respiratory effort such as coughing sneezing or laughing or by movements of the muscles of the trunk The diaphragm may move normally and quiet deep breathing may cause only a slight increase in the severity of the pain

The pain is accompanied by fever but there is little or no increase in the total leucocyte count Chills sweats nausea vomiting and hiccough are features in some cases Associated with the abdominal pain there is tenderness and rigidity of the anterior abdominal wall below the costal margin with moderate fullness of the abdomen and normal peristaltic sounds In some cases a to-and fro friction rub due to the perihepatitis can be heard Without specific treatment the symptoms and signs gradually subside over a period of 2 or 3 weeks

Examination of the chest may disclose the signs of a small pleural effusion which is confirmed by aspiration of small quantities of sterile fluid There may be transient icterus

The disease most often confused with this disorder is acute cholecystitis or

hydrops of the gall bladder The absence of severe constitutional symptoms and signs of pelvic inflammation aids greatly in the diagnosis The time between the symptoms suggesting pelvic inflammation and the onset of the signs of peritonitis varies from 1 to 3 weeks but in a few cases no signs of pelvic infection are present and symptoms have occurred as long as 5 years after an acute infection

In all patients suspected of having this infection a careful examination of the pelvis with smears and culture of the exudate should be made

Treatment —The treatment should consist of rest in bed and penicillin given systemically 15 000 to 5 000 units every 3 hours until the temperature has returned to normal and the symptoms and signs of acute infection have subsided

Systemic Gonococcic Infections

Bacteremia

It is not known how often the gonococcus invades the circulating blood from focal infections for the reason that blood cultures are made only in those patients who have an associated systemic reaction and then only if it is suspected that bacteremia exists That bacteremia has occurred in cases in which the infection is found at some distance from the original portal of entry there is no doubt The invasion of the blood by the gonococcus is not easy to demonstrate in spite of the fact that it must occur even as a transitory phenomenon in all cases in which metastatic lesions are present

Thus one sees bacteremia and metastatic lesions when the primary focus is in the genitourinary tract or the conjunctiva The former is much more common and the latter occurs only rarely in infants Once the gonococcus leaves its site of invasion and enters the circulating blood it tends to focalize most often in the joints tendon sheaths conjunctivae and heart valves and less often in other organs listed in Table 1 While the organism may focalize in any one of these locations it is a common experience in systemic infections to observe involvement of more than one organ although the outstanding features may be those of involvement of only one system such as the joints or the endocardium

As a means of distinguishing cases in which the invasion of the blood is transitory from those in which organisms can be isolated from the circulating blood on a number of occasions over a period of some days or weeks the clinical syndrome of gonococcemia has been described and is now well defined It has been pointed out by Blumer that the chief feature causing variation in the clinical picture of gonococcemia is the presence of endocarditis It is convenient and useful to describe the clinical picture of gonococcemia without endocarditis and of gonococcemia with endocarditis It must be appreciated however that the latter has been recognized oftener than the former It is well to remember then that when gonococci are isolated from the blood on more than one occasion endo

carditis should be suspected. An infection may be present on the heart valves without giving any signs of localization for several weeks. The diagnosis is suspected only when signs of valvular disease appear, or when there are embolic phenomena.

There are other important reasons for distinguishing between these two clinical forms of the disease. The prognosis is more favorable in patients without endocarditis and they are more amenable to treatment with penicillin.

Gonococcemia without Endocarditis

This form of gonococcic infection is characterized by the symptoms and signs of an acute septic infection, arthritis, a cutaneous eruption and the presence of gonococci in the circulating blood. In many respects these cases resemble those of acute or chronic meningococcemia, which is due to an organism that is biologically closely related to the gonococcus.

For some obscure reason this form of gonococcemia has been reported oftener in women than in men. This being so, it is often difficult to determine the time relation between the onset of the local infection and the invasion of the blood, since in many cases the local infection is latent. In some cases the symptoms appear during the acute phase of the gonorrhea, in others they have occurred after the acute phase of the gonorrhea has subsided. In several patients whom I have observed, the acute illness was preceded by an induced abortion or by excessive drinking and sexual activities, suggesting that traumatization of the tissues harboring gonococci was a strong predisposing factor. It has been stated that these cases are seen within 4 to 6 weeks after the initial infection, but there are many exceptions, since in most cases it is impossible to determine the onset of the initial infection.

The uterine cervix and the posterior urethra have been found to be the local focus, although cases have been described in the newborn in which the conjunctivae were involved first. In some of the fatal cases no primary focus is found even at necropsy.

Symptoms and Signs of Infection. — The onset of this disorder is characterized by a sudden departure from health with a shaking chill, high fever and sweats. The temperature is remittent and may fluctuate between 99° and 104° F. While these fluctuations may occur daily, the fever in some patients is intermittent in character and recurs only every 48 hours. In this respect the temperature curve may resemble that of a patient with meningococcic sepsis or malaria. With each elevation of the temperature there is usually a shaking chill. Headache, vomiting and diarrhea are frequent accompanying features. Two daily peaks of fever have been described in cases of gonococcic sepsis with or without endocarditis by Horder and Gow, Jochmann and Williams.

Arthritis — Associated with the chills fever and sweats there is a profound prostration and pains in the joints The arthritis is multiple and is accompanied by all the signs of acute inflammation although there may be a variable amount of periarticular swelling Accompanying the arthritis there may be tenosynovitis The course of the arthritis may not differ in any way from that observed in patients without bacteremia (see a subsequent page under Gonococcic Arthritis in Adults) When the exudate is abundant gonococci may be isolated from it

Cutaneous Eruption — One of the conspicuous clinical features is the skin eruption that is almost always present It is extremely variable in character and tends to occur over the extremities and trunk and to spare the face The commonest form of eruption is a macular papular or maculopapular rash which may become hemorrhagic and on which vesicles or pustules frequently appear Bullous eruptions and lesions like erythema nodosum have been observed also The eruption usually appears following the first bout of fever and it may become aggravated with each chill so that new lesions appear from day to day Cultures of the vesicles or pustules do not usually reveal the gonococcus although in a few cases such as those described by Reitzel and Kohl and by Klein gonococci have been reported

Bacteremia — The fourth and outstanding diagnostic feature is gonococcic bacteremia Isolating gonococci from the circulating blood clinches the diagnosis All blood cultures should be made from 10 to 20 c c of blood inoculated into broth of a pH of 7 6 to 7 8 and incubated *under reduced oxygen tension* Many of the failures to isolate gonococci from the blood in the past have been due to failure to incubate the cultures under reduced oxygen tension and to use the medium best adapted to the growth of gonococci

Aside from the isolation of gonococci from the blood an aid in the diagnosis of gonococcemia is the discovery of a local focus in the genital tract from which gonococci can be isolated or the isolation of the organisms from the joints or tendon sheaths or more rarely from the skin lesions

The examination of the heart is exceedingly important in all cases of gonococcemia for the reason that some patients develop the signs of destructive endocarditis which naturally changes the diagnosis and prognosis It has been noted time and time again that a soft systolic murmur was heard in patients who have recovered and in a rare patient who has recovered both a systolic and a diastolic murmur have appeared In the latter group the diagnosis of bacterial endocarditis is justified The spleen may be palpable but otherwise the physical examination is not essentially abnormal

In occasional fatal cases without clinical signs of endocarditis there have been vegetations on the heart valves without destruction or an endarteritis of the aorta with or without aneurysmal formation

Course of Disease — This is extremely variable and before the days of sul

fonamide or penicillin therapy patients were observed who had irregular fever lasting from 3 weeks to 5 months before recovery took place. Associated with the fever is a progressive anemia and leucocytosis, although in a few cases there has been no increase in the white cell count. Recorded counts vary from 8,500 to 22,000 and the predominating cell is the polymorphonuclear leucocyte.

Hemorrhages from the nose and into the gums and petechial eruptions over the skin, with or without thrombopenia, occur in some cases. Jaundice may appear as in one of my cases in which there was an associated cirrhosis of the liver. Other occasional features are metastatic conjunctivitis and aseptic meningitis.

Diagnosis. — The diagnosis rests on the isolation of gonococci from the circulating blood. The history of a recent or remote attack of gonorrhea, the onset of chills, fever, arthritis or tenosynovitis and a cutaneous eruption in a patient following abortion or signs of pelvic inflammatory disease or a urethritis should lead one to suspect the diagnosis. The finding of a local focus of infection associated with signs indicating a disseminated infection certainly suggests that bacteremia has occurred. If organisms can be isolated from the blood or metastatic lesions, the diagnosis is certain. It should be borne in mind that in many patients with a local focus of infection and metastatic lesions the blood is cleared of organisms within a short period of time, so that they cannot always be recovered. Moreover, it is frequently cleared before all the signs of the acute and active systemic infection have disappeared.

Prognosis. — In gonococcemia without endocarditis the prognosis is good. Most patients in whom the diagnosis has been established recover without any specific treatment, although the course may be a protracted one, lasting from 3 weeks to 3 months. At the present time the prognosis should be further improved by the early recognition of the disease and the use of penicillin or the sulfonamides.

Treatment. — This should be divided into two parts in accordance with a definite plan: general and supportive treatment and chemotherapy.

General and Supportive Treatment. — The patient should be given good nursing care. The diet should be liquid or semisolid and adequate in caloric content. The fluid intake should be such that the urine output is at least 1,000 to 1,500 c.c. a day. The headache and general symptoms of infection can be treated with sedatives and analgesics. Blood transfusions should be given if anemia develops, that is, a hemoglobin below 12 gm. per 100 c.c. or a hematocrit below 40 per cent. The joints should be protected against excessive motion if pain cannot be otherwise prevented.

Chemotherapy. — All patients should receive penicillin parenterally in amounts of 240,000 units a day in equally divided doses every 3 hours until all symptoms and signs of infection have disappeared. If there are large effusions into the

joints penicillin should be injected directly into the synovial cavity after withdrawal of the fluid

Summary — In brief gonococcemia without endocarditis is a type of systemic gonococcic infection with the following history A patient who has had a recent or remote attack of gonorrhea is seized suddenly with a chill high fever a skin rash and arthritis The chills and fever are recurrent and if the cause is unrecognized they may recur over a period of weeks or months A local focus of gonococcic infection usually is found in the genital tract and microorganisms are isolated from the circulating blood After an indeterminate period of time the blood is cleared of organisms the metastatic lesions in the skin and joints subside and the patient generally recovers unless foci of infection develop in the heart valves The treatment in all cases should be penicillin parenterally and it should be generally supportive

Gonococcic Endocarditis

The gonococcus is responsible for a few of the cases of infective endocarditis encountered in medical practice In clinics where there are a large number of negro patients the incidence is higher than elsewhere In Thayer's series it accounted for 11 6 per cent of 198 cases of bacterial endocarditis From Nashville Tennessee Williams reported that it accounted for 6 per cent of the cases of acute bacterial endocarditis In a collection of 1 000 cases of bacterial endocarditis Perry found that 4 6 per cent were caused by the gonococcus In general it can be said that the gonococcus is surpassed as a cause of infective endocarditis by the hemolytic and nonhemolytic streptococcus the staphylococcus and the pneumococcus How often it occurs during the course of gonococcic infection is unknown but it is infrequent since less than 200 proved cases have been reported in the literature This number does not reflect the true incidence of the disease for the reason that not all the cases are ever reported However it is safe to say that of the fatal complications of gonorrhea it is the commonest and of the metastatic lesions from a local focus it is surpassed in frequency only by arthritis tenosynovitis and the ocular metastases

Gonococcic endocarditis occurs five times as often in men as in women and it has been observed most frequently in the third decade of life In at least 90 per cent of patients the heart valves are normal prior to infection The time interval between the onset of the local gonococcic infection and the appearance of endocarditis has varied between 2 weeks and 14 years but in over a third of the cases in which reliable information is available it is 5 or 6 weeks In the cases in which the primary focus can be discovered (50 to 60 per cent) it has been in the posterior urethra the prostate or the fallopian tubes As in other cases of systemic gonorrhea the joints are involved frequently (50 to 60 per cent)

There are certain features in the history of patients with gonococcic endocarditis that are helpful in making one suspect the cause of the illness when the patient is seen initially First is the history of a local gonococcic infection in the past, and second is the occurrence of the symptoms and signs of an acute septic infection associated with acute arthritis The symptoms and signs of the arthritis may have disappeared before the patient is seen, but the other signs of an acute infection persist In any event in all patients with the symptoms and signs of an acute infection without localizing signs blood cultures should be made at once, because this examination may give one the first indication concerning the nature of the infective agent

Diagnosis — The diagnosis of gonococcic endocarditis is based on the following points 1 The symptoms and signs of an acute septic infection 2 The isolation of gonococci from the circulating blood and/or metastatic lesions 3 The development during the course of the infection of the signs of cardiac valvular disease especially those of aortic or pulmonary valvular insufficiency 4 The presence of embolic phenomena

Symptoms and Signs of Acute Septic Infection — The symptoms and signs indicating a general infection are chills fever sweats prostration and a rapidly developing anemia with leucocytosis These features may be accompanied by headache nausea and vomiting with diarrhea Associated with these symptoms and signs there is often a polyarthritis and occasionally an enlargment of the spleen due to acute splenic tumor Cutaneous subconjunctival or mucous membrane hemorrhages are seen in over half the cases, and epistaxis and hemorrhages into the gums and even the abdominal muscles may be conspicuous signs

The original focus of infection may be entirely latent or it may have disappeared In the male the history is more reliable In the female the association of the above symptoms during or following a pregnancy or an abortion or their appearance soon after a menstrual period may give a clue to the primary infection

In any patient then with the symptoms of an acute infection, multiple cutaneous hemorrhages arthritis and a local gonococcic infection in the genitalia the possibility of gonococcic endocarditis should be suspected even in the absence of cardiac murmurs

Development of Physical Signs of Cardiac Valvular Disease during the Course of the Infection — One of the most important diagnostic features of gonococcic endocarditis is the appearance of signs of valvular heart disease during the period of observation In at least 90 per cent of cases the gonococcus attacks previously normal heart valves When signs of valvular disease are present during the first examination one can often get some notion concerning its duration from the size of the heart In most cases of acute valvulitis the heart is normal in size A normal sized heart in the presence of the signs of aortic or mitral or pulmonary valvular disease is significant in that it suggests the recent onset of

valvular disease Of greater significance however is the appearance of signs of valvular disease for the first time during the course of the infection The commonest one is aortic insufficiency but mitral or pulmonary valvular insufficiency may be discovered In most cases these signs appear within 2 or 3 weeks after the onset of signs of systemic infection although they may not appear for 1 or 2 months after the onset of signs of systemic infection such as arthritis or other signs of a localized infection elsewhere

Embolic Phenomena — Infarction of the lung with pleurisy and/or blood spitting may be the only sign of embolism from the right side of the heart Embolism with infarction of the kidney, spleen or brain is not infrequent when the left side of the heart is involved Even the large vessels of the extremities may become plugged A search for signs of infarcts of the kidney pain in the loin or hematuria or spleen perisplenitic with upper abdominal or shoulder pain should be made Cutaneous hemorrhages should be looked for All these signs are significant because embolism is common and exceedingly important in supporting the diagnosis It should be stressed that pulmonary or cerebral embolism may occur some days or several weeks before the development of distinctive signs of valvular disease These features may give one the first indication of the underlying valvular infection as a source of emboli

Bacteremia — The isolation of the gonococcus from the circulating blood is important in supporting the diagnosis of endocarditis but it is not essential Acute and chronic gonococcemia without endocarditis undoubtedly occurs but the presence of valvular heart disease and the signs of embolism in a patient with the signs of an acute systemic infection and a history of gonorrhea are just as important in the diagnosis of gonococcic endocarditis as is isolation of the organism from the circulating blood All patients should have blood cultures and the blood should be cultured under conditions of reduced oxygen tension

Miscellaneous Associated Features — A few patients with gonococcic endocarditis have developed endaortitis or mycotic aneurysm of the aorta (see section Gonococcic Aortitis)

Jaundice is a feature in some patients when the infection is associated with cirrhosis of the liver, or when there are multiple pulmonary infarcts a rapidly progressive anemia or an associated central necrosis of the liver (see section Hepatitis)

Acute and subacute glomerular nephritis is exceedingly common and may be so extensive as to cause death in uremia with nitrogen retention Hematuria albuminuria and cylindruria give the clue to the diagnosis

Bilateral parotitis has been described by Steiner and Walton Diarrhea with bloody stools due to an associated *colitis* has been described by Thayer

Pericarditis occurring during the course of endocarditis is not infrequent since it is recognized at necropsy in about 40 per cent of cases

Electrocardiographic changes are characterized by evidence of myocardial damage with bundle branch and arborization block or with depressed T waves and slurring or widening of the QRS complexes. Myocardial abscesses are common findings at necropsy.

Pleurisy associated with pulmonary infarction and metastatic pneumonia are encountered occasionally, in particular in cases with endocarditis of the pulmonary valve leaflets.

Thrombopenic purpura hemorrhagica may be a feature of occasional cases (Lichtman).

Course of Disease. — The course of gonococcic endocarditis from the time of onset to its termination may vary from 4 to 9 weeks, although there are occasional cases in which the duration is as long as 8 months (Thayer). In a few reported cases death has occurred within 5 days after the appearance of valvular insufficiency. In another small group recovery occurs. In view of the fact that infection of the valves may be present without cardiac murmurs for as long as 2 or 3 weeks, it is highly desirable that all cases of systemic gonococcic infection be recognized as soon as possible and before signs of valvular damage have occurred in order that specific treatment may be started promptly. In the fatal cases the course of the disease is one of progressive failure with the symptoms of an acute infection, signs of profound intoxication, weight loss and anemia with death due to heart failure, anemia or embolism, alone or in combination.

Prognosis. — Before the days of hyperthermia occasional patients with gonococcic endocarditis recovered spontaneously. With the introduction of hyperthermia, with or without the use of sulfonamides, recoveries were reported also (Williams, Freund, Anderson and Lilly, Baehr). The introduction of penicillin furnishes another weapon that will be effective in some cases. Two of 4 patients treated with this drug, whose records I have reviewed, have recovered.

In brief, it can be said that gonococcic endocarditis presents a fairly characteristic clinical picture. The patient is usually a male in early adult life who has had gonorrhea in the past. After a varying interval of time, ranging from 2 go 4 weeks to as long as 14 years, there is a sudden departure from health with chills, fever and sweats, leucocytosis and a rapidly developing anemia. Pains in the joints appear in 25 to 65 per cent. of the patients and often precede definite signs of endocardial involvement. Since 90 per cent. of the cases have occurred in patients without previous valvular disease, there are no physical signs of valvular insufficiency at the onset of the infection in 9 out of 10 cases. However, evidence of valvular disease almost invariably appears before death. The time elapsing between the onset of symptoms and signs of a generalized infection and the development of signs of destruction of the valves is extremely variable. In some a characteristic murmur has been noted within 2 to 3 weeks after onset, although it is not known how long it has been present. In others the time between the

onset of symptoms and the development of valvular murmurs is 1 to 20 days In patients who have signs of an acute infection and who live one or two months without cardiac murmurs one may find evidence of an endaortitis at necropsy In general it can be said that after the onset of chills and fever patients who develop clinical signs of endocarditis usually do so within 2 or 3 weeks although in some who begin their clinical infection with arthritis 1 or 2 months may elapse before signs of valvular disease appear The valves most frequently involved are the aortic and mitral On the right side the pulmonary and tricuspid valves are about equally affected

Embolism to the spleen kidneys large peripheral vessels and brain is not infrequent Acute nephritis and pericarditis are fairly common occurring in 40 to 50 per cent of cases and death occurs from cardiac insufficiency anemia cerebral embolism or chronic infection

The isolation of gonococci from the circulating blood is of the greatest aid in diagnosis but the other features such as the development of valvular disease and embolic phenomena are important in cases in which bacteremia cannot be demonstrated

Treatment —In any discussion of the treatment of gonococcic endocarditis it is well to say something about its prevention In view of the observation that there is usually a period of several weeks to a month or longer between the initial infection and the appearance of signs of a systemic infection with endocarditis every attempt should be made to recognize localized gonococcic infection early and to treat every patient thoroughly with penicillin If this is done there are good reasons for believing that cases of gonococcic endocarditis will be prevented

Also it seems clear that the earlier one recognizes the systemic signs of gonococcic infection the sooner treatment can be started It should be stressed that once a patient with endocarditis develops a perforated valve and signs of valvular insufficiency the downward course is likely to be rapid In other words the development of the signs of valvular insufficiency is often a late manifestation of the infection All patients then with the signs of systemic infection without signs of valvular disease should be treated intensively with a presumptive diagnosis of endocarditis Finally all patients with valvular defects when first seen should be treated vigorously but the outlook in these cases may not be too good in view of the advanced stage in which the disease is recognized

Treatment should consist of 300 000 to 500 000 units of penicillin daily for 3 weeks or longer given in divided doses intramuscularly Blood transfusions should be used for the treatment of the anemia as indicated and a regime should be adopted to protect the heart by giving digitalis Acute nephritis if it exists should be treated by appropriate measures Only experience will give the answer as to the results of modern chemotherapy in these cases To repeat early and

intensive treatment with penicillin should be carried out in every patient with gonococcic infection

Arthritis in Adults

Gonococcic arthritis is the commonest metastatic lesion of gonorrhea Although it usually follows a genital infection it may follow ophthalmia in the newborn vulvovaginitis in childhood or even a proctitis It is impossible to state with any degree of accuracy how many patients with gonorrhea develop arthritis, since the statistics vary from one clinic to another, from one hospital to another and from one specialist to another The incidence has been recorded as varying from 1 to 10 per cent of patients with gonorrhea This is perhaps too high Certainly it can be said that with the introduction of specific chemotherapy, sulfonamides and penicillin the incidence of gonococcic arthritis has been greatly reduced It is seen oftenest today in patients who have had a local infection that was unrecognized before the onset of the arthritis and in those who have been inadequately treated These observations serve to stress the importance of the early diagnosis of local gonococcic infection and the prompt and intensive systemic treatment with chemotherapeutic agents as a preventive measure

Age and Sex — Gonococcic arthritis is seen at all ages, but since gonorrhea is most frequent in persons between the ages of 15 and 30 years arthritis is encountered oftenest during this age period It is generally agreed that gonococcic arthritis is seen oftener in men than in women in a ratio of 3 or 4 to 1 It should be stressed, however that gonococcic arthritis may be present in the newborn in infants or in children as well as in older people

Predisposing Factors and Time of Occurrence — It is not known why some patients with gonorrhea develop arthritis and others do not There may be some variation in the invasiveness of the different strains of gonococci as well as differences in the natural resistance of the host but both these factors are difficult to define specifically and objectively Our previous studies (Spink and Keefer) suggested that both factors might be operative in a given case

The association of menstruation pregnancy and trauma to the tissues harboring the organisms is often thought to be related to the spread of the infection The factor of trauma to infected mucous membranes has been stressed by Pelouze The observations that arthritis follows meatotomy the passage of a sound the opening of a paraurethral sinus or a vigorous prostatic massage serve to support this view Also it is clear that a large number of patients with arthritis are found among those who subject themselves to traumatic influences in the presence of active infection of the urethra Gentleness in treatment of local infections and early systemic treatment with penicillin should greatly reduce the incidence of arthritis

Trauma to the joints or the tendon sheaths may in some mysterious way influence the localization of infection following its spread from a local focus

Arthritis tends to appear within 10 days to 3 weeks after the initial infection The interval is however much longer in some cases than in others and often the relation is difficult to determine because the initial infection has been latent It is unknown why there should be this latent period just as it is unknown why some patients develop arthritis and others do not

Pathological Change in Joints — The essential pathological feature in gonococcic arthritis is an acute synovitis with an intense inflammation of the sub synovial tissues and secondary destruction of the cartilage In the 2 cases studied at post mortem by Keefer Parker and Myers the pathological changes varied in severity In one case gonococci were isolated from the synovial fluid and microörganisms that were tinctorially identical with gonococci were seen in the stained tissues In the second case the inflammation was not so intense and microörganisms were neither isolated by culture nor found in the fixed and stained tissues These two types of cases are identical with those that are seen clinically namely patients with an infected synovial fluid and those with a sterile fluid These changes have been described elsewhere but will be repeated here

In the case in which microörganisms were found the synovial membrane had been completely destroyed and replaced by granulation tissue containing numerous lymphocytes polymorphonuclear leucocytes macrophages and plasma cells In the deeper layers of the synovia there was a perivascular infiltration of lymphocytes

The sections stained for bacteria showed numerous gram negative cocci which were identified as gonococci since this organism had been recovered from the tissues by cultural methods There was little change in the cartilage overlying the articular surface

Examination of the synovial membrane from the joint in which no gonococci were demonstrated showed a proliferation of the synovial membrane with an increase in thickness and collections of polymorphonuclear leucocytes In the subsynovial tissue layer or connective tissue layer there was a marked infiltration with polymorphonuclear leucocytes lymphocytes and macrophages with intense congestion of the blood vessels An occasional macrophage filled with blood pig ment was seen In several foci there was a partial loss of the superficial synovial cells with a deposit of fibrinous thrombi In places the collagen and polymorphonuclear leucocytes appeared necrotic A careful search of the tissue stained for bacteria failed to reveal their presence

It appears that the inflammatory lesions in the synovial membrane in patients with sterile synovial fluid are much less intense than in those with infected fluid In the former the surface layer of the synovia remains intact and shows no areas

of destruction while in the latter there is complete destruction of the synovial lining with replacement by granulation tissue In the one case the conspicuous lesions are beneath the surface of the synovia, whereas in the other they extend to the surface and produce complete destruction of the superficial cells

Destruction of the articular cartilage varies considerably in different cases of gonococcic arthritis depending apparently on the joints involved It is most pronounced in the wrist and phalangeal joints, the hip and the ankle joints It is less conspicuous in the knee joints This may be accounted for in part by the fact that in the knee joint large amounts of fluid collect whereas in the other joints mentioned there are a great many white blood cells and relatively small amounts of synovial fluid Studies on the antitryptic content of synovial fluid and the tryptic activity of white blood cells in digesting cartilage suggest that the articular cartilage in the knee joint is protected in many cases by the presence of a large effusion of fluid which contains antitryptic substances When the exudate is thick and purulent and contains a relatively small amount of synovial fluid, the opportunities for the destruction of cartilage are great

Ankylosis of joints associated with gonococcic arthritis is due to periarticular fibrosis or adhesions between the articular cartilage In the case of the knee joint stiffness and limitation of motion are often due to adhesions between the patella and the femur True bony ankylosis is rare except when the wrist or hip joints are involved

Diagnosis — The diagnosis of gonococcic arthritis depends on the isolation of the gonococcus from the synovial fluid In such cases no doubt exists Unfortunately this is not possible in all cases so that the diagnosis rests on the following evidence 1 A history of a recent attack of gonorrhea 2 Evidence of a local gonococcic infection in the genitourinary tract 3 The characteristics of the arthritis and of the synovial fluid 4 A positive gonococcic complement fixation test in the blood and or synovial fluid 5 The clinical course of the disease and the features associated with the arthritis

A history of a recent attack of gonorrhea is obtained in men oftener than in women However a history of sexual exposure or promiscuity is important and when this behavior has been accompanied by overindulgence in alcohol it is especially significant The occurrence of trauma to the mucous membranes of the genitalia preceding the arthritis is suggestive and the same can be said for overindulgence in alcohol since it is well known that a latent gonococcic infection often is activated by excessive drinking and sexual excitement Also the onset of arthritis in women soon after a menstrual period or in a female patient who has had attacks of low abdominal or right upper quadrant pain may give one a clue

Isolation of Gonococci from a Local Focus of Infection — A thorough examination of the exudate from the genital tract by smears and cultures is a most im

portant part of the examination The material should be cultured at the time of the examination A suitable medium should be used and the cultures should be incubated under reduced oxygen tension The isolation of the gonococcus from the urethral exudate or prostatic fluid or from the uterine cervix or other regions of the genitalia is highly suggestive of the cause of an arthritis

Characteristics of the Arthritis and the Synovial Fluid — Gonococcic arthritis is an acute and extremely painful form of joint disease Its onset usually is abrupt and it is often preceded by a chill and high fever It is more often polyarticular than monoarticular and any joint of the body may be involved The usual distribution is shown in Table II The tissues overlying the joints often are red hot and edematous and movement of the joints causes exquisite pain When the tendon sheaths are involved the surrounding tissues are swollen and the movement of the tendons causes great pain Accompanying the acute inflammation there is a rapid wasting of the muscles in the neighborhood of the joints this is very striking about the shoulder or knee joints The pain often is so severe that it can be controlled only by using codeine phosphate along with salicylates Indeed in my own experience large doses of salicylates alone fail to control the pain in the acute stages of the disease

The synovial cavities are distended with exudate This is most striking in the case of the knee joints In many other joints of the body where the synovial cavities are not so easily distended the exudate may be less in amount and the tendency toward destruction of the cartilagenous surfaces appears to be greater This is especially true of the bones of the hands and feet

There is nothing characteristic about the roentgen ray appearance of the affected joints There is soft tissue swelling and atrophy of the bone and in some cases destruction of the cartilage and underlying bone Involvement of the periosteum especially about the joints of the fingers and feet is very important in a few cases

The synovial fluid from patients with gonococcic arthritis has all the characteristics of an exudate with an increase in the total protein content Gonococci can be cultivated from these fluids in only 25 to 35 per cent of cases In these the diagnosis is obvious The failure to cultivate these organisms does not however exclude a gonococcic infection It is not clear why one fails to cultivate gonococci from the synovial fluid in all cases Certainly it is safe to assume that the reaction in the joints is due to the deposit of microorganisms in the synovial tissues or subsynovial tissues or to the deposit of the irritating chemical substances resulting from the autolysis of organisms The latter hypothesis cannot be proved with certainty in man However it should be pointed out that an acute arthritis can be produced in horses following the injection of sterile filtrates containing only the autolyzed products of the gonococcus commonly known as gonococcus toxin The same products are highly irritative to the human urethra

TABLE II

SUMMARY OF CLINICAL FEATURES IN 140 CASES OF GONOCOCCIC ARTHRITIS

1 Sex — Males		104	
Female		36	
2 Polyarthritis		107	
Monoarthritis		33	
3 Joints Involved			Tenosynovitis
Knees		127	4
Ankles		56	32
Wrists		44	19
Metacarpo-phalangeal		7	6
Shoulders		25	
Metatarsal and phalangeal		27	6
Fingers		31	4
Hips		23	
Elbows		20	
Lumbar part of spine		14	
Toes		19	
Sacro iliac		8	
Heel		7	
Cervical part of spine		6	
Dorsal part of spine		4	
Sterno-clavicular		3	
Costo-sternal		2	
Temporo-mandibular		3	
Olecranon bursa		1	
Acromio-clavicular		1	
4 Associated Features			
Conjunctivitis		21	
Abscess of tendon sheath		2	
Death		7	
Endocarditis	2		
Glomerulonephritis	1		
Intercurrent pneumonia	3		
Progressive gonococcic infection	1		
Iridocyclitis		4	
Glomerulonephritis		2	
Pregnancy		4	
Bacteremia		5	
Recovered	3		
Died	2		
Endocarditis		2	
Keratodermia blennorrhagicum		4	
Sterile meningitis		1	

and conjunctiva It is possible then that the rapid autolysis of organisms in the tissues about the joints accounts for the inflammation or that chemical substances derived from the gonococcus in a local lesion cause irritation in certain tissues of the body

The total cell count of the synovial fluid varies with the stage of the disease and with other factors such as the presence or absence of microorganisms In general it can be said that the count is likely to be higher and with more polymorphonuclear cells in the infected fluids than in the sterile ones There are exceptions to this statement but our own experience lends great support to it The total cell count in infected fluids may vary from 7 000 to 236 000 per cubic millimeter with 75 to 100 per cent polymorphonuclear cells whereas in the sterile fluids it varies from 1 600 to 120 000 per cubic millimeter with 45 to 100 per cent polymorphonuclear cells The sugar content in infected synovial fluids is lower than that of the blood whereas in sterile effusions it is the same

In general it can be said that the most distinctive feature of the synovial fluid is the presence of gonococci The other characteristics are in no way different from those of acute inflammatory lesions in the joints due to other causes The synovial fluid should be examined in all cases of arthritis for the presence of gonococci as well as for other features

The Gonococcic Complement Fixation Test —A positive gonococcic complement fixation reaction is present in approximately 85 per cent of cases of gonococcic arthritis The reaction of the blood serum and that of the synovial fluid simultaneously collected usually are identical The examination of the synovial fluid offers little if any advantage over that of the blood serum The test is of the greatest value in patients who have a sterile synovial fluid and in those who fail to show an obvious local focus of infection A positive reaction often suggests that the arthritis is due to a gonococcic infection and a further search for a focus of infection is required In our own experience the reaction usually becomes positive within 2 weeks after the onset of the arthritis and remains so for as long as 6 months to 1 year after the infection has become established

The finding of a positive complement fixation reaction does not establish the diagnosis since like all other serological reactions it must be interpreted as a part of the total clinical picture A positive reaction indicates infection with the gonococcus It may be a part of the past history or the present illness The presence of a positive complement fixation reaction along with other features of the disease that are compatible with the clinical diagnosis of gonococcic arthritis is thus of great value in supporting the diagnosis

Clinical Course and Features Associated with the Arthritis —The presence of gonococcic arthritis should be suspected in any person who has an acute monoarticular or polyarticular arthritis that begins abruptly The arthritis is acute and may involve any joint of the body and often it is preceded by a chill and

high fever Usually it is associated with tenosynovitis, especially about the wrist or ankle joints and there is an associated bilateral metastatic conjunctivitis in about 15 per cent of the cases

In the vast majority of cases one can isolate the gonococcus from either the synovial fluid or a local focus of infection in the genitourinary tract, and in at least 85 per cent the gonococcic complement fixation reaction in the blood is positive The examination of the synovial fluid for bacteria and other characteristics is important in the diagnosis

The isolation of the gonococcus from the synovial fluid or from the tendon sheaths clinches the diagnosis The other features mentioned above including the isolation of the gonococcus from a local focus or a positive gonococcic complement fixation reaction and the associated features of the disease are exceedingly significant in the final diagnosis when gonococci cannot be found in the synovial fluid

In brief the course of events in patients with gonococcic arthritis may be summed up as follows

Subsequent to a gonococcic infection of the urethra or uterine cervix or less often of the conjunctiva an acute polyarticular or monoarticular arthritis appears It is often abrupt in onset and usually is ushered in by a chill and high fever The signs of infection are accompanied by pain in the joints and all the signs of an intense inflammation involving the periarticular tissues and the synovial membranes There is pain redness swelling and tenderness of the joints with limitation of motion The arthritis is more often polyarticular than monoarticular although after the initial onset with polyarthritis only one or two joints may continue to show inflammation Any joint in the body may be involved but the knees, ankles wrists and metatarsal and metacarpal joints are those oftenest involved The distribution of the arthritis and other lesions that we observed several years ago are shown in Table II

Associated with the arthritis there is often tenosynovitis about the wrists and ankles and in some cases the tendon sheaths are involved without any conclusive signs of arthritis In my own experience tenosynovitis is much more common in patients with gonococcic arthritis than in those with other types of arthritis and it is a valuable diagnostic sign The onset of the arthritis may be preceded by an acute respiratory infection so that this feature temporarily may obscure or confuse the diagnosis In the vast majority of cases the arthritis begins within 10 to 20 days after the onset of the gonorrhea However acute arthritis due to the gonococcus may occur months or years after an attack and in some case it develops after the original infection of the genitourinary tract has healed entirely In women the arthritis not infrequently occurs when the local infection is latent and has caused no local symptoms In a few cases gonococcic arthritis is associated with pregnancy and in a rare case the arthritis follows an

operation for the removal of the prostate or a pelvic operation in patients who have had gonorrhea many years previously (Spink and Keefer, Fraser)

At the onset there is fever leucocytosis and an elevation of the corrected sedimentation rate The duration of the fever is variable and it may persist for a few days to several weeks depending on the severity of the infection and associated lesions The process is most intense within the first few days of onset and does not tend to migrate from one joint to another unless there is trauma to the local focus of infection in the genitourinary tract Exacerbations of the arthritis are observed after a vigorous prostatic massage or following a reinfection Frequently the process becomes most conspicuous in one or more joints

The symptoms of the arthritis if not treated specifically with chemotherapy persist for an indeterminate period and many patients formerly were disabled for 60 to 90 days or longer

Accompanying the acute process in the joints and tendon sheaths there is a rapid wasting of the muscles supporting the affected joints Occasionally the inflammation spreads from the joints to the muscles but in many patients the atrophy of the muscles is not accompanied by signs of acute inflammation

Demonstrable bacteremia is unusual unless there is an associated endocarditis or the accompanying features of an acute septic infection gonococcemia (see section Gonococcemia without Endocarditis) When the arthritis is a feature of gonococcemia there are certain features to be looked for These are a skin eruption and an intermittent or remittent tertian type of fever

When the arthritis is associated with endocarditis the appearance of a cardiac murmur or the signs of embolism in the lungs or in the organs supplied by the greater circulation is important (see Gonococcic Endocarditis)

An uncommon form of cutaneous eruption accompanying gonococcic arthritis is keratodermia blennorrhagicum (see Cutaneous Manifestations of Systemic Gonococcic Infections) Another rare feature of gonococcic arthritis in the absence of endocarditis is acute hemorrhagic glomerulonephritis (see Renal Complications of Gonococcic Infections)

The ocular signs of the gonococcic infection are most interesting and important, since they aid in the diagnosis and when there is an iridocyclitis the seriousness of the disease is obvious As related under the discussion of the Ocular Manifestations of Systemic Gonococcic Infections (see that heading on a later page) the commonest sign is a metastatic catarrhal conjunctivitis which occurred in 15 per cent of our cases Iridocyclitis on the other hand occurs much less often It was present in 4 of 140 patients with arthritis

It can be said then that an acute polyarthritis or an acute monoarthritis associated with tenosynovitis a history of gonococcic infection, conjunctivitis or iridocyclitis or a cutaneous manifestation resembling psoriasis is always suggestive of gonococcic arthritis

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It can be said then that an acute polyarthritis or an acute monoarthritis associated with tenosynovitis a history of gonococcic infection conjunctivitis or iridocyclitis or a cutaneous manifestation resembling psoriasis is always suggestive of gonococcic arthritis

Differential Diagnosis — In view of the fact that it is not always a simple matter to isolate the gonococcus from the synovial fluid or from a local focus of infection at the time the arthritis is observed, it is often necessary to rely on the history, clinical course and laboratory tests such as the gonococcus complement fixation test in order to establish the diagnosis.

There are certain diseases other than gonococcic arthritis in which the arthritis may be associated with a skin eruption, a urethritis or conjunctivitis. The two most important diseases in which the arthritis is associated with urethritis and conjunctivitis are post enteric arthritis and Reiter's disease.

Post enteric or Post dysenteric Arthritis — These cases are confused with gonococcic arthritis because of the associated urethritis and conjunctivitis. The main features that distinguish this disease from gonococcic arthritis are a history of a previous diarrhea and failure to isolate the gonococcus from the synovial fluid, the urethral exudate or the conjunctiva. The story usually is somewhat as follows. During or following an attack of acute bacillary dysentery or an attack of diarrhea in which it has been impossible to isolate *Bacillus dysenteriae*, the patient develops an acute arthritis. It usually occurs during convalescence from the dysentery, generally appearing between the tenth and thirteenth days after the onset of the illness. The joints most often involved are the knees, hips and hands. With the onset of the arthritis there is fever of indeterminate duration which may continue for 1 to 3 weeks. The local condition of the joints is characterized by pain, tenderness and swelling with limitation of motion and occasional periarticular swelling with signs of tenosynovitis.

There is some elevation of the skin temperature but redness of the skin is absent. The synovial fluid is light yellow, slightly turbid and contains moderate amounts of mucin with leucocytes varying in number from 1 to 10 000 per cubic millimeter, with polymorphonuclear cells predominating. The fluid is sterile but it may contain agglutinins against the infecting strain of dysentery bacilli. Recovery usually is complete with restoration of normal function of the joints in spite of the fact that symptoms may be severe and continue for as long as 2 or 3 months.

The diagnosis is based on the history of an acute bacillary dysentery followed by an arthritis of the large joints with a sterile synovial fluid and a sterile exudate from the urethra and conjunctivas. The absence of a positive gonococcus complement fixation reaction and a positive agglutination test aid in establishing the diagnosis.

Reiter's Disease — Under Reiter's disease or a syndrome of unknown etiology characterized by urethritis, conjunctivitis and arthritis Bauer and Engleman have described 6 personally observed cases and present a review of the literature. This disorder was first described in 1916 by Reiter and other cases have been described since then.

The disorder occurs always in young male adults The first symptom usually is urethritis but it may be conjunctivitis This is followed by monoarticular arthritis or polyarticular arthritis of the weight bearing joints The triad like that of gonococcic arthritis is complete within 10 to 21 days after the initial symptoms The relative absence of constitutional symptoms is a striking feature and fever if present is only of moderate degree The urethritis may be complicated by prostatitis vesiculitis hemorrhagic cystitis and shallow ulcerations of the penis

The conjunctivitis is purulent in character and in some cases superficial punctate keratitis episcleritis or iritis has been noted Neither the ocular manifestations nor the urethritis persist as long as the arthritis

The arthritis is the most persistent and disabling feature of the disease It is sudden in onset and extremely painful There is nothing specific about the synovial fluid since the cytological and chemical characteristics of the fluid are similar to those occurring in other forms of infectious arthritis The synovial membrane on examination after biopsy shows intense hyperemia and foci of acute inflammatory cellular infiltration Roentgen ray films of the joints show bone atrophy and occasional circumscribed areas of subchondral atrophy

The arthritis runs a self limited course lasting 1 to 5 months Recurrences occur in about one fourth of the cases and may involve any or all of the three systems Recovery is complete

There is nothing diagnostic in the laboratory data There is leucocytosis and an increased sedimentation rate The exudates are sterile The gonococcus complement fixation reaction is negative

The absence of signs of gonococcic infection in any area by smear or culture is the most important discriminating feature

Kerato conjunctivitis Sicca — This rare disease should cause very little confusion in diagnosis since it occurs almost invariably in women without a history of urethritis It is characterized by an absence of tears and saliva so that there is a kerato-conjunctivitis dryness of the mouth recurrent attacks of parotitis and moderate enlargement of the lymph nodes in the preauricular region The arthritis is not associated with effusion of fluid into the joints but with pain and stiffness The conjunctivitis is secondary to dryness of the eyes and is not due to an inflammation that is associated with an increased amount of exudate However the arthritis and conjunctivitis may at first glance suggest other diseases producing these two features

Other forms of arthritis that may be confused with gonococcic infection are rheumatic fever acute rheumatoid arthritis acute pyogenic arthritis and syphilitic arthritis

Rheumatic Fever —The disease that is chiefly confused with gonococcic arthritis is rheumatic fever with arthritis Inasmuch as there are absolutely no specific

diagnostic tests available for the diagnosis of rheumatic fever, it must be recognized from the history, physical examination and clinical course. The history of rheumatic fever in adults frequently discloses attacks earlier in life and the occurrence of a sore throat, tonsillitis or an acute respiratory infection preceding the onset of the arthritis. One should not be misled by this history, however, since Myers and I found that at least 15 per cent of patients with gonococcic arthritis date the onset of their illness from an acute sore throat. In general, however, the arthritis of rheumatic fever tends to be migratory and relapsing. It persists in one joint for 1 to 8 days and then progresses from one joint to another unless it is adequately controlled and treated by salicylates. The associated features of the disease are of aid, for example, the presence of cardiac valvular disease with pericarditis and pleurisy, the presence of abnormalities in the electrocardiogram and the course of the disease. The isolation of gonococci from the synovial fluid settles the question in any doubtful case. However, the isolation of the gonococcus from the urethra may show an associated infection as is indicated by the clinical course in some cases (Myers). In spite of certain difficulties in differential diagnosis that may be present early in the course of the disease, it is usually possible to make the diagnosis after following the patient for a short period of time.

Rheumatoid Arthritis. — In the acute form of rheumatoid arthritis one may encounter iridocyclitis and conjunctivitis or scleromalacia perforans, i. e. a scleritis with thinning of the sclera so that the choroid shows itself as a dark border about the cornea. In advanced cases it may perforate. In this disorder the recurrent nature of the arthritis and ocular lesions with characteristic deformities of the joints and the absence of positive evidence of gonococcic infection are important in the differential diagnosis.

Pyogenic Arthritis. — The type of pyogenic infection that may mimic gonococcic infection is the chronic relapsing form of meningococcemia with bacteremia, arthritis and a cutaneous eruption. The eruption may be indistinguishable from that seen in gonococcemia, since the lesions in both infections may be like erythema nodosum or maculopapular or hemorrhagic and vesicular lesions. The only means of distinguishing between the two infections is careful bacteriological study of the organisms isolated from the circulating blood and the absence of a focus of infection in the genital tract.

The joint symptoms associated with *erythema multiforme* may be accompanied by conjunctivitis and stomatitis. There is usually no effusion into the joints and no urethritis.

Syphilitic Arthritis. — Occasionally a patient with a previous history of gonorrhea and syphilis develops arthritis that is due to the syphilitic infection and not to the gonococcic infection. Acute syphilitic arthritis has been described by several authors and reviewed most recently by Kling. The type most likely to

be confused with gonococcic arthritis is the acute form associated with fever a cutaneous eruption painful lymphadenopathy and moderate eosinophilia That this form is due to syphilis there is no doubt since *Treponemata* have been isolated from the synovial fluid by Chesney and his associates The response of the arthritis to active antisyphilitic treatment may be dramatic

Treatment — As soon as the diagnosis is established treatment with penicillin should be started One hundred thousand to 00 000 units should be injected intramuscularly in divided doses every day and this should be continued for at least 7 days It is also necessary in some patients with an infected synovial fluid to inject penicillin directly into the joint cavities This can be done by dissolving 50 000 units in one or more cubic centimeters of normal physiological salt solution and injecting it directly into the joints

In patients who have sterile synovial fluid the course of the disease following chemotherapy is satisfactory but it may not be dramatic in the sense that there is rapid improvement

Inasmuch as recovery from the arthritis is likely to require some weeks the patient often presents the clinical picture that is so frequent with any chronic infection loss of weight anemia and atrophy of the muscles about the infected joints Every effort should be made therefore to provide a liberal intake of food to treat the anemia if it is present with iron and blood transfusions and to care for the patient symptomatically as regards pain and discomfort

The following procedures should be carried out during convalescence An effort should be made to re-establish normal muscle tone about the affected joints through active and passive motion exercises the arches of the feet should be given support if the patient has been confined to bed for a long period of time and instructions should be given regarding prophylaxis against venereal disease

The most important feature of the treatment of gonococcic infection is the prevention of systemic infections These infections can be reduced by early prompt and intensive treatment of a local focus with penicillin and by avoiding the manipulations and procedures that encourage spread of infection

Arthritis in Infants

The reason for discussing gonococcic arthritis of the newborn and infants independently of the disease in adults is to point out certain differences in the clinical features the portal of entry and the severity of the disease Cases have been reported as occurring sporadically or in epidemics arising in hospitals (Parrish Console and Battaglia Cooperman and Holt) In the newborn the infection of the child is acquired oftenest from the mother and while the first manifestation of infection may be an ophthalmia neonatorum in some cases there is no obvious portal of entry until the joints become involved The problem is then one of

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location of the hips Contractions of the joints soft tissue hyperplasia and residual foot and wrist drops were present in some cases

In brief the destructive lesions of the joints are more striking in infants than in adults Soft tissue suppuration is more common and foot and ankle drop are much more frequent

Treatment — The treatment of these patients from the beginning should consist of systemic treatment with penicillin in amounts of 100 000 units daily aspiration of the joints and injection of penicillin directly into the cavities Orthopedic measures should be used also to protect the joints relieve pain and prevent deformities All patients should be confined to bed and given analgesics for the relief of pain and sedatives to produce sleep Codeine phosphate and aspirin for the pain and barbiturates for sleep are the most useful drugs

The affected joints should be placed at absolute rest to prevent pain and to relieve the associated muscle spasm The local application of heat is helpful in relieving pain The synovial fluid should be removed for culture and to relieve the distention of the joint capsule

Tenosynovitis

Infection of the tendon sheaths is a frequent finding in patients with systemic gonococcic infections It may occur alone or as is commoner in association with arthritis It may be either suppurative or non suppurative and the gonococcus frequently can be isolated from the fluid The suppurative form of the disease has been described fully in recent years by Birnbaum and Callander and an excellent account of the non suppurative variety was given by Strandberg in his discussion of arthritis In our own experience suppurative tenosynovitis occurred in 2 of 140 patients with arthritis and the non suppurative form was observed in approximately 50 per cent of the cases The tendons oftenest involved are those about the ankles and those of the hands wrists and feet

The primary focus is in the genital organs or the eyes and the inflammation of the tendon sheaths appears about the same time as the arthritis

The onset frequently is abrupt with localized pain swelling and edema over the affected part Movement of the tendon in its sheath is extremely painful and in some cases it may be difficult on superficial examination to discriminate between the tenosynovitis and the associated arthritis Localized edema and redness of the overlying skin are common The swelling of the tendon sheath may be localized and there may be signs of periostitis and destruction of the underlying bone as was the case in one of our patients with tenosynovitis of the tendon of the index finger

The diagnosis can be made from localizing the infection in the tendon sheath and finding evidence of gonococcic infection by aspiration of fluid or finding evidence of infection elsewhere

sepsis of the newborn In other cases the disease is spread from one infant to another through the medium of infected rectal thermometers, wash basins and laundry Once a local infection of the vulva or rectum becomes established bacteremia may follow arthritis being a special feature The urethra is not involved in males It should be repeated that one very extraordinary feature is the occurrence of arthritis without any obvious portal of entry That the disease in infancy may be extremely serious is indicated by the fact that 14 of 26 cases reported by Holt in 1905 were fatal

The clinical features described by Cooperman in a hospital epidemic illustrate how serious and crippling the disease may be The arthritis occurred in 53 of 67 infected infants The history was somewhat as follows Within 8 to 9 days after birth there was fever fluctuating between 99° and 102° F, a skin eruption over the trunk and extremities swollen fingers and toes and superficial abscesses in various parts of the body This is the clinical picture that is usually present in patients with gonococcemia (see under Gonococcemia without Endocarditis) Within a day or two after the onset of the fever the infants are extremely ill they refuse to eat and cry when handled and diarrhea with pus in the stools and purulent discharges from the vagina are noticed That proctitis is present in some cases is attested by the purulent rectal discharges by positive smears and cultures from the rectum and by the development in some patients of ischiorectal abscesses

The arthritis is more often polyarticular than monoarticular, and the joints most often involved are the wrists knees shoulders ankles toes fingers hips elbows and tarsals Pain and great swelling of the joints and periarticular tissues with edema and redness of the surrounding tissues are striking and swelling of the palm with wrist drop accompanied all the cases reported by Cooperman in which there was involvement of the wrist joints The inflammation was a periarthritis or a suppurative or non suppurative arthritis In the patients with marked periarticular swelling frequently there was no clear evidence of involvement of the joints The tissues involved included the muscles, tendons and ligaments about the joints

In suppurative lesions of the joints the bursas about the shoulders and knees often contained pus In the non suppurative cases the joint spaces were filled with turbid exudates

An extraordinary feature was the flaccid palsies of the extremities with extreme muscular atrophy This was said to be due to edema of the peripheral nerve trunks about the involved joints In some cases at least 8 months to 1 year was required for complete recovery to take place

Foci of osteomyelitis are much commoner in infants than in adults They were observed in the shafts of the long bones such as the humerus and ulna Destruction of the acetabulum of infected hip joints resulted in spontaneous dis

the vertebrae humerus tibia ulna or other bones have been present with destruction While some of these cases have been associated with arthritis others such as the case reported by Woolsey have involved the vertebrae without evidence of joint involvement The destruction of bone may be considerable and abscesses may develop in the surrounding tissues The course of the disease may be chronic but healing finally takes place if recovery occurs Osteomyelitis of the long bones apparently is commoner in infants than in adults In the cases studied by Cooperman the lesions healed without operation after a number of months

Periostitis

Osteoperiostitis of the small bones of the hands and feet is not uncommon in gonococcic infections but periostitis of the long bones is much less frequent Cases proved by bacteriologic examination are rare although the one described by Watts showed great proliferation of the periosteum of the diaphysis of the femur with all the signs of an acute inflammation and with gonococci in the exudate Incision and drainage of the periosteum and surrounding tissues were followed by healing Many of the older cases were described without bacteriological proof In general it can be said that periostitis of the long bones is not common In some there is an associated infection of the marrow cavity with foci of osteomyelitis

Osteoperiostitis of the Os Calcis (Painful Heel)

It should be remarked at once that not all cases of osteoperiostitis with exostoses on the inferior surface of the os calcis are due to gonococcic infection That some of them are there is no doubt since Baer has isolated the gonococcus from some of the cases in which he excised the inflammatory exostoses on the inferior surface of the os calcis at the tubercle

In the proved cases the patients invariably are males the process is bilateral and the main complaint is pain on walking which is very severe and in most patients incapacitating It is referred to the attachment of the plantar fascia and there is thickening and swelling at the point of the attachment of the fascia to the bone The x ray film shows exostoses

The *treatment* consists in the surgical removal of the spurs and this usually results in prompt relief of symptoms and in cure

Perichondritis

Inflammation of the perichondrium of the ears ribs and thyroid cartilage of the larynx has been described in occasional cases Myers and I have observed two patients in whom the larynx was involved in association with arthritis

The outlook is good although in some cases the convalescence is slow In a few adhesions occur between the tendon and the vaginal covering so that deformities take place Incision and drainage of the tendon sheaths is necessary

Bursitis

Infection of the bursas by the gonococcus is less frequent than that of the joints or tendon sheaths Occasionally the prepatellar, subcrural trochanteric and tarso-metatarsal bursas and those over the tuberosity of the ilea are involved Bursitis is seen during the acute or subacute stage of the local infection, and the process may be kept active owing to movement and trauma Suppuration is infrequent and after an indefinite period of time complete resolution takes place with or without fibrosis or scar formation The gonococcus may be recovered from the exudate in the bursa as reported by Dieulafoy

There is one form of bursitis that deserves special comment since it causes a painful heel and may be confused with gonococcic osteo-periostitis of the os calcis or with retromalleolar bursitis This form involves the bursa between the anterior surface of the Achilles tendon and the posterior inferior surface of the os calcis The term achillodynia" was attached to this ailment by Albert The involvement of these bursas usually is bilateral

Clinically there is severe pain over both heels, which is aggravated by motion Examination of the affected parts shows a localized tender swelling between the tendon and the os calcis Limitation of motion is obvious, and in some acute cases there are signs of acute inflammation with local redness and edema

The diagnosis may be suspected from the history of gonorrhea and the symmetrical nature of the bursitis and made by aspiration of the bursa and culturing the exudate

This type of bursitis is distinguished from retromalleolar bursitis by the localization of the pain and swelling and from osteo-periostitis by x ray examination of the os calcis in the lateral position which demonstrates an exostosis on the inferior surface

The outlook in these cases is favorable with complete restoration of function, but as in patients with gonococcic arthritis there may be exacerbations with recurrence of fresh attacks of gonorrhea

The *treatment* consists of the relief of pain by rest sedatives and the application of local heat during the acute stages Penicillin (50 000 units) should be injected directly into the bursa after the aspiration of fluid

Osteomyelitis

Metastatic foci of infection in the bones are infrequent in gonococcic infection There are scattered reports in the literature however in which osteomyelitis of

been the calf the thigh the psoas major the latissimus dorsi the posterior tibial and the masseter Abscesses may develop in previously injured muscle with hematoma formation

The *treatment* consists of incision and drainage of the abscess with intensive penicillin treatment of 100 000 units daily until complete healing has occurred It is not known whether aspiration of the abscess and intensive systemic penicillin would be effective but in view of the success of the treatment of other pyogenic abscesses in this manner it is worthy of a trial

Lymphadenitis

Enlargement of the lymph nodes in the region of the infected joints may be a conspicuous feature in some cases of gonococcic arthritis especially the form of the disease which runs a protracted course Forkner has isolated the gonococcus from the lymph nodes in such cases The nodes do not suppurate

Ocular Manifestations of Systemic Gonorrhea

Gonococcic ophthalmia in the newborn is a well recognized form of ocular infection due to the implantation of gonococci in the conjunctiva at the time of birth from an infected mother It is occasionally encountered in adults or in children who have accidentally contaminated the conjunctiva Infected material may get into the conjunctiva at a surgical operation or the infection may be spread from the urethra to the conjunctiva by means of the fingers or by other means The ocular manifestations that concern us here are those that are metastatic or a part of a systemic invasion from a local focus of infection usually in the genital tract Although these forms of the disease are widely recognized by ophthalmologists the internist who is seeing patients with arthritis will encounter a number of cases and should be familiar with the various features Their presence assists the diagnosis of systemic infection and they require special treatment

Conjunctivitis — Metastatic catarrhal conjunctivitis usually is bilateral and generally occurs along with the other manifestations of systemic gonorrhea especially arthritis It was a feature of 21 of 140 cases of gonococcic arthritis reported by Spink and myself It is observed oftenest in males between the ages of 20 and 30 years and in some patients it is the initial symptom of a systemic infection According to Byers who has written an excellent monograph on the subject of the ocular manifestations of gonorrhea the conjunctivitis may occur as the only manifestation of systemic gonorrhea or it may precede or accompany the other signs of systemic infection

The conjunctivitis is practically always bilateral and both eyes are involved

In the case of perichondritis of the ear cartilage described by Fischer, there was burning pain in the ears with redness of the skin and thickening of the cartilages especially at the periphery There was induration of the part, and passive motion was painful Healing was complete with only slight residual thickening

In our cases of perichondritis of the larynx the patients complained of pain on swallowing and tenderness over the larynx There was no demonstrable redness of the skin or swelling The inflammation subsided without any signs of suppuration

Gonococcic abscess between the costal cartilages has been recorded by Baker and Carter in a patient who had acute gonococcic arthritis and a protracted fever lasting 38 days The abscess was about 1 cm in diameter and was overlying and extending into the perichondrium of the cartilage of the anterior surface of the 7th rib about 2 cm from its juncture with the sternum It contained many gonococci

Myositis and Muscular Atrophy

It is convenient to discuss these two forms of muscular disorder together Gonococcic myositis as a matter of convenience may be described as a suppurative and a non suppurative variety They are both caused by the deposits of gonococci in the muscles Lorenz described the cases of non suppurative myositis in an adequate fashion as did Ware A recent report of suppurative myositis by Linner describes and reviews this form of the disease

In the non suppurative form the myositis almost invariably occurs in association with arthritis and the muscles involved are in the neighborhood of the affected joints usually in the muscles of the thighs The onset is featured by pain in the affected part which is followed within a few days by localized induration of the muscle which is tender to palpation and depending on the depth of the lesion, the indurated area is covered by normal skin or there may be edema over the localized muscle group In the case reported by Ware organisms were stained in the serous exudate that was obtained on incision and the muscle showed an interstitial myositis In general these instances of localized non suppurative myositis regress so that the muscles ultimately return to normal function Permanent scarring with fibrosis has been described and even ossification has been seen

Suppurative gonococcic myositis has been described recently by Linner in a patient with urethritis and arthritis In a review of the literature Linner points out that in most of the cases there had been a genital infection a few weeks or even several years before the onset of the myositis In many cases the abscesses occurred by direct extension from an infected joint, and these were commoner than metastatic muscle abscesses without arthritis The muscles affected have

With prompt treatment both local and general recovery usually follows although there may be some permanent damage to the structure of the eye

Dacryoadenitis — The cases that are caused by direct extension of the infection from the conjunctiva are generally unilateral and proceed to suppuration whereas the rare cases that are metastatic and bilateral end in resolution

Optic Neuritis — According to Byers the metastatic form of neuroretinitis is bilateral and associated with retinal edema The prognosis is guarded but the outlook is good

The *treatment* of all these cases should be managed with the cooperation of a skilled ophthalmologist Systemic treatment with penicillin is indicated in all cases for at least 7 to 10 days

Cutaneous Manifestations

For convenience the skin manifestations of gonococcic infections may be discussed under three groups those associated with bacteremia without endocarditis (gonococcemia) those associated with bacteremia and endocarditis (gonococcic endocarditis) and those associated with gonococcic infections without bacteremia

Bacteremia without Endocarditis — The cutaneous eruptions occurring during the course of gonococcemia have been described by a number of observers since they are a prominent feature in this form of gonococcic infection In the case report by Bakst Foley and Lamb lesions like erythema nodosum were prominent and from a review of the literature by these observers and others it is plain that the eruption may be maculopapular hemorrhagic vesicular or pustular on a papular base or the lesions may be nodular or urticarial in type In an occasional case thrombopenic purpura hemorrhagica accompanies the infection

The cutaneous lesions associated with gonococcemia tend to occur in crops and there are outbreaks with recurrent bouts of fever The fever may be protracted and there is often an associated arthritis Gonococci are difficult to cultivate from the lesions and it is only in isolated cases that success has been achieved In any patient with protracted fever arthritis and a skin eruption such as is mentioned above blood cultures should be made and material from the lesions should be cultured Finally a search should be made in the genitourinary tract for signs of a local gonococcic infection

Bacteremia with Endocarditis — During the course of gonococcic endocarditis petechial hemorrhages in the conjunctiva the ocular fundi and the skin occur in about half the cases It is a curious fact that the types of cutaneous eruptions that are frequent in gonococcic infection without endocarditis are rarely seen in patients with endocarditis This may be of some aid in differential diagnosis and hence in prognosis however it is not possible at this time to explain the mechanism for the difference in the types of eruption Petechial or cutaneous hemorrhages therefore should make one consider bacterial endocarditis

simultaneously In a few of the reported cases it is unilateral It may begin in one eye and be followed by involvement of the other within a period of 24 hours to 2 weeks The most striking feature in most cases however, is the symmetrical character of the disorder

The onset is characterized by both subjective and objective signs of catarrhal inflammation of the conjunctiva In a few cases the subjective symptoms are much less striking than the objective signs As a rule, however, burning smarting lacrimation and photophobia are complained of, and one finds signs of an acute catarrhal conjunctivitis involving both the palpebral and ocular conjunctiva The lower lid is involved oftener than the upper and in fact the latter frequently is spared In a few cases the inflammation is confined to either the palpebral or the ocular conjunctiva Edema of conjunctiva and chemosis of the bulbar portion occurs in about half the cases and edema of the lids is seen in about 10 per cent The discharge usually is slight and varies in character from seromucous to mucopurulent In general the discharge is scanty and mucoid and smears and cultures of this material are sterile

When only the conjunctiva is involved the course of the disorder usually is self limited lasting about 2 weeks Recovery is complete without any damage to the other parts of the eye In about one third of the cases the cornea or the iris may become involved within a period of 24 hours to 6 weeks most often, however, within 2 weeks

In any case then of arthritis or of local infection of the genitourinary tract one should look carefully for signs of ocular involvement in the form of conjunctivitis or kerato conjunctivitis or iritis

The metastatic nature of the conjunctivitis may be determined by the mildness of the subjective and objective symptoms the absence of any history of infected material having come in contact with the conjunctiva the symmetrical character of the lesion and its appearance along with other manifestations of systemic gonococcic infection

Relapses are likely to occur with reinfection, but as a rule without reinfection recovery is complete

Keratitis — Keratitis as a manifestation of systemic gonorrhea commonly is bilateral, central in location and superficial in nature Usually it is associated with conjunctivitis

Iridocyclitis — Involvement of the uveal tract is much less frequent than involvement of the conjunctiva It was observed in 4 of our 140 cases of arthritis This may be unilateral or bilateral and in some cases is accompanied by a bilateral catarrhal conjunctivitis In the initial attack it may be bilateral but in subsequent or later attacks it tends to relapse or to recur in one eye with fresh attacks of gonorrhea The inflammation precedes follows or accompanies other manifestations of systemic gonorrhea It may be the sole feature of a systemic infection

intensive systemic treatment with penicillin should be carried out Local treatment with penicillin ointment may be a good adjuvant

Renal Complications

There are three recognized renal complications of gonococcic infection pyelonephritis acute glomerulonephritis with or without an associated bacterial endocarditis and renal infarction secondary to bacterial endocarditis

Pyelonephritis pyonephrosis pyelitis and cysto-pyelitis secondary to gonococcic infection of the genitourinary tract have been studied by a number of physicians These infections are single or mixed with other organisms such as *Escherichia coli* or *Staphylococcus aureus* In order that a diagnosis may be established it is necessary to demonstrate the gonococcus by cultural and immunological reactions It is important to distinguish between pyuria due to infection of the lower urinary tract and that resulting from infection of the kidney parenchyma There is some evidence that the existence of a pathological lesion of the kidney preceding the gonococcic infection predisposes the kidney to infection

The second type of renal lesion accompanying gonococcic infection is an acute glomerulonephritis Several years ago Spink and I reported a case in which the patient died in uremia following an acute glomerulonephritis which was associated with a gonococcic infection of the seminal vesicles prostate posterior urethra and epididymis The patient developed all the symptoms and signs of acute glomerular nephritis while under observation in the hospital for the treatment of the gonococcic infection The nephritis was characterized by hypertension albuminuria cylindruria hyposthenuria hematuria oliguria increasing nitrogen retention leucocytosis anuria and uremia and ended in death There was no endocarditis at necropsy

Most of the cases of glomerulonephritis associated with gonococcic infection have been described in patients with gonococcic endocarditis The lesions in the kidney are those of an acute hemorrhagic glomerulonephritis and necrotizing arteritis The lesions in the glomeruli may be quite distinct from the focal embolic lesions which are present also in some cases with endocarditis In Thayer s cases nephritis was present in 55 5 per cent and death in uremia was not infrequent

Inasmuch as nephritis is so common in patients with endocarditis and so infrequent in those without it the appearance of signs of this disease should lead one to suspect a complicating bacterial endocarditis in any patient with gonococcic infection

Renal infarction due to emboli from the valves of the heart may be suspected in a patient with bacterial endocarditis and gross hematuria If it is accompanied or preceded by unilateral pain in the loin and associated nausea and vomiting

Keratodermia Blennorrhagicum — A rare form of cutaneous eruption in gonorrhea is keratodermia blennorrhagicum It resembles psoriasis and from the characteristics of the skin eruption alone it is impossible to distinguish the two It is invariably associated with a gonococcic infection of the genital tract and gonococcic arthritis The pathogenesis of this type of skin eruption is not known Many attempts have been made to culture gonococci from the lesions but according to Downing only 5 reports gave positive results and it is questionable whether more than one of these cases was a true keratodermia blennorrhagicum

Some observations by Dr Smead of Parke Davis Company as described to me by Ralston may be significant in this report During the course of immunizing horses against gonococcic toxin it has been noted that there develops in many horses an arthritis and signs of inflammation of the skin with edema formation There is a marked hyperkeratosis of the skin over the extremities with a heaping up and flaking off of the epithelium of such thickness that it fills out between the hairs to their tips This scaly mass may become one quarter to one half inch in thickness and once it is removed it tends to recur very rapidly The hair falls out readily around these scaly masses When the scales are removed, one finds numerous small incrustations that resemble dried serum exuding from small breaks in the skin These cutaneous lesions clear quickly, if the animal is given a rest from toxin injections for 2 or 3 weeks One of the most interesting features of these cases is that they are produced in horses by the injection of sterile filtrates from cultures of the gonococcus and are associated with arthritis (see Gonococcic Arthritis) It is possible then that the hyperkeratotic dermatological lesions in man may be produced by the products of the gonococcus just as they are in horses Here is a lead for the study of the pathogenesis of such cases in man

In human beings keratodermia blennorrhagicum has almost always been observed in men The first cutaneous lesion is a well defined papule This is followed by crusting due to necrosis in the corium where there is lymphocytic infiltration The lesion becomes pustular and increases in size The necrosis and crusting also increase from the center to the periphery As the acute process subsides the pustular ring disappears and is replaced entirely by a crust, which ultimately separates leaving a smooth hyperpigmented skin Similar lesions have been observed in the mucous membranes of the mouth The lesions are widespread over the body trunk extremities palms and soles

These cases must be distinguished from *psoriatic arthritis* and this can be done usually by finding evidence of a gonococcic infection of the genital tract

The *treatment* is directed toward the gonococcic infection with penicillin given systemically Care should be taken to prevent secondary infection of the skin In some patients the lesions have remained for 3 months before complete recovery took place In view of the occasional finding of the gonococcus in such lesions

intensive systemic treatment with penicillin should be carried out Local treatment with penicillin ointment may be a good adjuvant

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the diagnosis is more certain Focal embolic glomerulonephritis may cause only microscopic hematuria and may cause no signs of advanced renal insufficiency

Hepatitis

Hepatitis occurring during the course of gonococcic bacteremia endocarditis and multiple pulmonary infarction has been recorded by Blumer and Nesbit The patient was a young man who had had gonococcic urethritis followed by polyarthritis the signs of pulmonary valvular endocarditis and persistent jaundice with slight enlargement of the liver The blood cultures were negative, but the diagnosis of endocarditis and an associated hepatitis was confirmed at necropsy The patient ran the course of a septic infection with weight loss a high leucocytosis and cardiac insufficiency with edema and ascites and died in coma approximately 8 weeks after the onset of the illness The liver showed an acute inflammatory process and a fine fibrosis or cirrhosis Many lobules were destroyed There were also many pulmonary infarcts which may have contributed to the jaundice and hepatic disease

Jaundice was present in 5 patients with gonococcic endocarditis reported by Williams and in cases recorded by Steiner and Walton Thayer Lichtman and Silvestrini Icterus was a striking feature in a case of gonorrheal bacteremia studied by Spink and myself and it has been made the special topic for discussion in gonococcic infections by Popper and Wiedman It is also a feature of some cases of gonococcic perihepatitis (Stanley)

The mechanism of the production of icterus in these cases is not always clear and it is certainly not uniform In several cases there was an associated cirrhosis of the liver Hepar lobatum was described by Williams and in our case there were clinical signs of cirrhosis of the liver with hepatomegaly splenomegaly transitory ascites and edema and cutaneous spider angiomata In other cases there has been cardiac insufficiency with central necrosis of the lobules and in a few there have been pulmonary infarcts associated with right sided valvular endocarditis In Lichtman s case there was a rapid destruction of blood with a progressive anemia and thrombocytopenia There may be signs of an acute inflammation of the liver as described by Blumer and Nesbit Popper and Wiedman have suggested the hypothesis that the products of the gonococcus in the form of so-called gonotoxin are histiotoxic for the liver but there is no support for this contention from experimental studies

In view of the reported cases when jaundice occurs during the course of a gonococcic infection one should suspect a latent cirrhosis of the liver with bacteremia or an associated bacterial endocarditis with or without pulmonary infarcts Other contributing factors may be cardiac insufficiency and excessive blood destruction When jaundice occurs during the course of a local infection,

it may be due to some intercurrent infection such as infectious hepatitis Whether the toxic products of the gonococcus can cause liver damage alone remains to be proved

Liver Abscess

In the patient described by Baker and Carter a solitary gonococcic abscess of the liver was discovered at necropsy During life the patient had symptoms of an acute infection with high irregular fever leucocytosis of 18 000 to 33 800 per cu mm a progressive anemia a moderate enlargement of the liver and gonococcic bacteremia No organisms were found in the genitourinary tract although there was a history of gonococcic urethritis 19 years previously The onset of the illness was characterized by fever chills and diffuse abdominal pain At the time of the first examination there was diffuse abdominal tenderness with muscle spasm especially in the right upper quadrant Exploratory laparotomy failed to disclose the liver abscess In brief the symptoms of an acute infection with gonococci in the blood without localizing symptoms of infection other than moderate enlargement of the liver should lead one to suspect the liver as a source of the infection in spite of its rarity Other cases of gonococcic abscess of the liver have been described by Bousfield and Roughton

Pericarditis

This has been reported more often by the pathologist than by the clinician and it is seen most frequently in association with endocarditis It was present in 40 per cent of Thayer s cases The exudate may be fibrinopurulent or hemorrhagic and the inflammation may arise in one of several ways When the exudate is fibrinopurulent the pericardium usually is infected from the heart muscle or by direct extension of the infection from the base of the aorta In some cases it is impossible to trace the source of infection and it is probably hematogenous in origin The infection of the base of the aorta may be associated with aneurysmal formation mycotic aneurysm When the exudate is hemorrhagic it generally indicates that a mycotic aneurysm has leaked into the pericardium

The clinical diagnosis can be made by hearing a friction rub or detecting signs of a pericardial effusion When pericarditis is associated with endocarditis the signs may be evident before those of valvular disease appear In any patient with gonococcic infection who develops the signs of pericarditis the question of an associated endocarditis or mycotic aneurysm of the aorta should be raised

Aortitis

Gonococcic infections of the aorta occur as mycotic aneurysms associated with endocarditis as aneurysms without associated infective endocarditis and as

infections of the aortic wall without aneurysmal formation vegetative aortitis In 1933 Aschner reported a case and collected 8 other proved cases from the literature More recently Currens and Faulkener have described additional cases In essence the clinical course resembles that of endocarditis, with which this condition generally is associated In view of the fact that these aneurysms may leak into the pericardial sac pericarditis and hemopericardium are complications The appearance of pericarditis during the course of the infective endocarditis may suggest that the pericardium has become infected from an aneurysm at the base of the aorta However this is only indicative since pericarditis may be observed during the course of endocarditis secondary to an abscess of the heart muscle or as a metastatic lesion

There are no distinctive diagnostic features indicating the presence of a gonococcic infection of the aorta Embolism to the organs in the systemic circulation without evidence of aortic or mitral valvular disease may be suggestive The signs of visible pulsation in the first and second intercostal spaces to the right of the sternum associated with the signs of aortic insufficiency, may indicate mycotic aneurysm of the aorta in accordance with the experience of Stengel and Wolferth

Pneumonia

Gonococcic pneumonia is seen as an embolus type of pneumonia in the course of some cases of gonococcic sepsis Intercurrent pneumonia due to other organisms may be encountered in patients with chronic gonococcic sepsis or arthritis Spink and I observed several such patients In any event it is a feature that accompanies other manifestations of infection and does not occur as an independent or isolated feature of gonococcic infection

Pleurisy

As in other forms of sepsis pleurisy may occur during the course of the infection owing to an underlying focus in the lung This focus may be an infarct or a pneumonitis and it is invariably associated with bacteremia endocarditis or pericarditis

The involvement of the peritoneal surface of the diaphragm by the gonococcus can give symptoms of diaphragmatic pleurisy with pain referred to the shoulder that is aggravated by respiratory effort In some of the cases there is an associated pleurisy with effusion The demonstration of pelvic inflammatory disease in such patients aids in the diagnosis (see in section Subdiaphragmatic Peritonitis)

In the case of pleural effusion reported by Jacob the fluid contained eosinophils and basophils whereas the blood showed no increase in these cells The finding

of many eosinophils in gonococcic inflammation is not uncommon in chronic inflammation of pelvic tissue Here the infiltration generally is localized but occasionally it is reflected in a slight increase in the eosinophils in the blood The significance of the eosinophilia is unknown

Thrombophlebitis

Local gonococcic thrombophlebitis affecting the veins of the genitalia is an extremely rare complication of gonorrhea According to Pelouze it is seen only in very severe cases in which the penis has been subjected to the trauma of masturbation or coitus In the review by Payenneville it is stated that the thrombosis nearly always involved the superficial veins of the penis particularly the dorsal vein Pain in the penis radiating into the groin is present There are dusky red lines following the course of thick cordlike subcutaneous veins Very rarely the deep cavernous or periprostatic veins become occluded When this occurs there may be extensive death of tissue with gangrene of the glans and anterior urethra The prognosis in the cases with superficial thrombosis is good and its treatment consists of local application of heat and freedom from trauma

Thrombophlebitis may be associated with arthritis in rare cases It is stated that the internal saphenous vein on the right side is oftenest involved

Meningitis

In view of the recent reports (Branham Mitchell and Brainin Steiner and Marvin and Wilkinson) there is no doubt that the gonococcus occasionally invades the meninges and causes meningitis In a survey of 500 strains of gram negative diplococci isolated from the spinal fluid in patients with meningitis and studied by Branham and her associates 1 per cent were found to be gonococci Steiner was able to collect from the literature 10 cases of meningitis due to the gonococcus In his own case the patient had an associated pelvic peritonitis

In a patient observed by Spink and myself there were signs of meningitis with an increase in the total cell count of the spinal fluid but no organisms were isolated by culture

There are no distinctive features of gonococcic meningitis and according to Branham and others in the cases reported to them there was no obvious primary focus In others (Steiner Marvin and Wilkinson Spink and Keefer) there was evidence of a primary gonococcic focus in the pelvis or elsewhere The disease with which it is oftenest confused is meningococcic meningitis and without careful bacteriologic study and without signs of a local gonococcic infection the distinction cannot be made

According to Marvin and Wilkinson recovery has been reported in half the

infections of the aortic wall without aneurysmal formation vegetative aortitis In 1933 Aschner reported a case and collected 8 other proved cases from the literature More recently Currens and Faulkener have described additional cases In essence the clinical course resembles that of endocarditis with which this condition generally is associated In view of the fact that these aneurysms may leak into the pericardial sac pericarditis and hemopericardium are complications The appearance of pericarditis during the course of the infective endocarditis may suggest that the pericardium has become infected from an aneurysm at the base of the aorta However this is only indicative, since pericarditis may be observed during the course of endocarditis secondary to an abscess of the heart muscle or as a metastatic lesion

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In the case of pleural effusion reported by Jacob the fluid contained eosinophils and basophils whereas the blood showed no increase in these cells The finding

Here again the pathogenesis is not clear and since the cases are infrequent it is difficult to study many of them for factors causing the nerve lesions

PSYCHOLOGICAL REACTIONS

The psychological reactions of patients to their infection are often a problem to the physician They must be considered as a part of the treatment of the individual patient

THE ASSOCIATION OF GONORRHEA AND SYPHILIS

Any patient who acquires gonorrhea from sexual contact may acquire syphilis at the same time a fact that is well established This has become of increasing importance with the introduction of penicillin for the treatment of gonorrhea and syphilis because a certain number of patients with gonorrhea recover promptly following penicillin treatment and the development of the signs of syphilis is delayed or completely masked All patients then should be followed for several months following treatment for gonorrhea and repeated blood examinations should be made to exclude latent syphilis masked by early penicillin treatment

cases Their patient recovered following the giving of sulfanilamide whereas Steiner's patient recovered following the administration of antimeningococcic serum

Today penicillin would be the drug of choice in the treatment of these cases

Cerebral Embolism

Cerebral embolism occurs in about 15 per cent of patients with gonococcic endocarditis In a few cases it has been a feature of the disease before distinctive signs of valvular destruction have been noted In the cases with hemiplegia there is often an aseptic meningitis (Solomon Hurwitz Woodall and Lamb)

Pulmonary Embolism

In gonococcic endocarditis of the pulmonary or tricuspid valves pulmonary embolism and infarction are not infrequent Indeed pleural pain with a friction rub and cough with hemoptysis may be the initial clinical signs directing one's attention to the heart as a site of infection

Occasionally pulmonary infarcts arise from emboli in the veins of the legs or from the veins of the pelvis

Myelitis Meningomyelitis and Neuritis

There have been a number of reports of gonococcic myelitis or meningomyelitis occurring in association with gonococcic infection In some cases only the lower extremities are involved and recovery has taken place (Phifer and Forster) unless there is a serious and uncontrolled infection of the urinary tract with pyelonephritis In others the lesions may be more extensive and if they are located high in the cervical cord with extension to the medulla, the disease may prove fatal in a brief period of time (Courville) In Courville's case there was an irregular softening process in the spinal cord with infiltration with leucocytes There was an acute degeneration in the parenchymatous and interstitial elements of the cord It was not possible to demonstrate the gonococcus in these lesions

Clinically the cases have been described in patients with a gonococcic urethritis The onset is characterized by pain and paresthesia in the legs and trunk pains in the back impairment of sphincter control and a paraplegia of the flaccid type Lesions may develop at a higher level so that spasticity replaces atony We certainly need more information about the pathogenesis of these cases

Neuritis with wrist or foot drop has been described in infants with extensive involvement of the periarticular tissues and extensive muscular atrophy has suggested involvement of the nerve trunks as well as the muscles (Cooperman)

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CHAPTER III-A

CHANCROID

By FRANCIS M THURMON

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Synonyms — Soft chancre ulcus molle chancre mou

Definition — Chancroid is an acute specific infectious ulcerative disease caused by the streptobacillus of Ducrey (*Haemophilus ducreyi*) A painful inflammatory suppurative ulceration at the site of inoculation often accompanied by painfully swollen and suppurative regional lymph structures is characteristic The ulceration always sharply localized may be multiple Autoinoculation sites are not uncommon Occasionally phagedenic destruction occurs The skin mucous membrane and deeper structures of the genitalia most frequently are involved Extragenital lesions are rare

History

Ducrey[1] in 1889 was the first to recognize and describe the causative organism of chancroid a small gram negative bacillus which now bears his name There is no doubt that the streptobacillus of Ducrey (*Haemophilus ducreyi*) is responsible for chancroid and for the buboes which sometimes are associated with the initial lesion

Unna[2] in 1892 substantiated the observation of Ducrey and described the chains of bacilli seen in smears from the ulcerations In 1901 Besancon Griffon and Le Sourd[3] using blood medium successfully cultured *H ducreyi* and Tomasczenski[4] in 1903 reproduced the disease in human beings with pure cultures

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In 1913 Ito[7] working with Carl Bruck at Neisser's clinic devised a specific intradermal test for chancroid using the Ducrey bacillus vaccine. The diagnostic value of this test was confirmed later by Reenstierna[8], working with a serum containing antibodies of the Ducrey bacillus. Today this test is spoken of as the Ito-Reenstierna reaction.

Frei[7] surveying the entire subject up to 1927 wrote "... another biologic diagnostic measure, the intracutaneous test with specific vaccine, has already achieved universal recognition. This procedure, developed by Ito and more recently again employed by Reenstierna, Frei, Nicolle and Durand, Rivalier, Couvert, Dubreuilh and Broustet and other authors, surely represents the most interesting and firmly established biologic phenomenon in the field of investigation of streptobacilli since the introduction of the cultural method."

Wolf and Sulzberger[8] were the first to use the specific diagnostic skin test in the United States in 1931 wherein they employed the European Ducrey bacillus vaccine known as dmelcos. These authors repeatedly called to the attention of American physicians the diagnostic value of this test.

Cole and Levin[9] in 1935 being unable to obtain the commercial dmelcos vaccine in this country prepared an antigen from chancroidal bubo pus. There is now available a Ducrey[10] vaccine of American manufacture.

The voluminous literature throughout the world readily attests the method of preparation of the vaccine, the performance and interpretation of the skin test and its value. In this connection the excellent study of Knott and associates[11] forcefully calls attention to the likelihood of cross biologic reactions, yielding transient false positive results when two or more genitoinfectious diseases are coexistent in the same lesion. The life long presence of a positive skin test with the Ducrey bacillus vaccine is a well established fact. In 1937 Topley and Wilson[12] summarized the bacteriology of the causative agent. Additional references regarding the essential features of chancroid are contained throughout the present presentation. The enormous extent of the literature is amazing and due credit cannot be given in this discussion to all contributors on the subject.

Treatment of chancroid was revolutionized in April 1938 when Hanschell[13] first described the astounding and dramatic effect of the sulfonamide preparations on chancroid. In the few intervening years since Hanschell's original report an adequate literature has accumulated to indicate clearly that all other methods of therapy are obsolete. Even now the prophylactic use of sulfonamide derivatives is being reported and due caution with regard to their possible toxic effects is stressed.

INCIDENCE

Chancroid is a fairly common genitoinfectious lesion endemic in world wide proportion with a tendency toward great prevalence in warmer climates and

seaports and among populations where personal hygiene and promiscuity are on a casual plane Its demonstrable incidence in the female is much less frequent than in the male the ratio man to woman being approximately 10 1 Certain observers[14, 15] believe that the *H ducreyi* may exist as a non pathogenic saprophyte on normal mucosa of the vaginal introitus and cervix and thus the woman potentially is a symptomless carrier of the disease

In the United States chancroid seems to be more prevalent in the South particularly among the negro population In Alabama in 1932 the incidence of chancroid per thousand inhabitants was 12 75[16] Greenwald[17] reviewing chancroidal infections over a nine month period in 1942 in a Station Hospital in Virginia where the ratio of colored soldiers to white was approximately 1 5 found the incidence of Ducrey infection to be 73 colored to 3 white primary admissions or an approximate ratio of 130 1 The ratio of chancroid in white to colored troops of the United States in 1918 was 1 8 94[18]

Raushkolb[19] in a civilian clinic found a 66 per cent incidence in negro patients Sullivan[20] in an analysis of the reports of the Surgeon General of the United States Public Health Service with not all states reporting chancroid cites the year 1937 when 4 271 cases of chancroid were reported In Boston from 1930 to 1944 the number of cases of chancroid in my clinic of dermatology and syphilology of the New England Medical Center which averages 32 000 patient visits yearly chiefly whites was 2 per thousand occurring chiefly in white patients

The average annual rate per 1 000 among enlisted men of the United States Army[21] for chancroid for the years 1914 through 1929 was 9 4 while that of enlisted men in the United States Navy and Marine Corps[22] over the corresponding sixteen year period was 31 08 Sailors traveling over various parts of the world seem to be a class among which this disease is quite frequent

Coulter[23] in 1937 reviewing the alarming incidence of chancroid in British Naval Units based on Alexandria stated venereal disease is rampant in Egypt as it was in olden times and further chancroid infections are predominant and seem to be regarded (by the native population) very lightly as little more than a common cold

Reports from other countries show the infection to be a not uncommon disease of variable incidence In Cuba from 1925 to 1932 Pardo Castello[24] reported 27 16 cases of chancroid per thousand in his clinic of dermatology and syphilology Various authors state the disease is endemic in Italy and Northern Africa especially Morocco

During the period 1925 to 1937[25] in England and Wales the cases of chancroid in males reported to the Minister of Health averaged approximately one tenth the reported incidence of new infections with syphilis In the female during this entire twelve year period only 276 instances of chancroid were reported as compared with 83 676 cases of syphilis

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croids originate from the small types and extend peripherally to destroy large areas or to form an ulceration following a bubonulus

In women the commonest sites of involvement are the labia minora clitoris fourchette and vestibule While the vagina seldom is involved the cervix occasionally may be the site of chancroidal infection Due to the proximity of the vulva and anus and in those with perversive tendencies anal infections are of frequent occurrence In this region the lesions are exquisitely painful and occasionally are confused with ulcerated thrombotic hemorrhoids

Extragenital infections are rare Chancroid of the lip tongue tonsils and palate following cunnilingus have been observed Chancroidal infection of the finger especially the index finger as occurring in physicians nurses and medical attendants *professional chancroid* fortunately are rare This type of extragenital lesion is painful Patients sometimes accidentally infect their fingers while applying dressings to a genital lesion and in turn the infected digit may autoinoculate other parts of the body In this respect lesions of the breast neck and conjunctiva have been observed

Complications

The *chancroid bubo* usually is unilateral and is present in approximately 50 per cent of *H ducreyi* infections of the male genitalia The regional lymph nodes become enlarged and tender and occasionally are accompanied by constitutional symptoms of fever and anorexia The nodes become matted together and eventually fluctuant Pain and inflammation accompany the swelling and the overlying skin is erythematous Spontaneous rupture and healing may occur but in some cases the ulceration spreads peripherally to form a giant chancroid The period required for the development of an inguinal bubo varies greatly and may range from a few days up to several weeks following the appearance of the ulcer or even appear after the primary le ion has healed Strenuous exercise delayed therapy inaccessible lesions improper medical procedures, all predispose to the development of these *bubones*

Lymphangitis from chancroid is rare This complication is characterized by nodular thickenings of the dorsal lymph channels of the penis These nodules may undergo spontaneous involution or progress to suppuration with formation of abscess *bubonuli*

Mixed infections are not uncommon complications of chancroid Fusospirochetosis [7] almost invariably is a superimposed infection and often enhances the ulcerative and destructive qualities of the chancroidal infection Complicating granuloma inguinale or lymphogranuloma venereum suggest the advisability of searching for Donovan bodies and performing a Frei test on all chancroids of long standing

The complication of syphilis and chancroid acquired simultaneously is indeed

The reported incidence of chancroid in the Armed Forces of both England and the United States indicates clearly that the disease is prevalent in the Canal Zone the Philippines Hawaii China and India Lahiri[26] in 1942 stated chancroid is a common disease in India both in hospital and private practice In Bihar he found it equally distributed among the poor and rich, and they formed about 25 per cent of cases attending the Venereal Outdoor of the Patna Medical College Hospital

Clinical Manifestations

A break in the integument during exposure with an infected medium is essential to the transmission of *Haemophilus ducreyi* A short incubation period usually one to three days occasionally as long as three weeks is characteristic for the disease The earliest lesion as judged by transfer inoculation sites is a macule which becomes a papule and then a pustule The pustule ruptures and a small painful inflammatory, sharply circumscribed, non indurated shallow ulcer is exposed At this stage the inoculation sites frequently are multiple The lesions spread by peripheral extension and by coalescence of adjacent ulcers The larger a lesion grows the more irregular its contour becomes Usually by the time the patient presents himself there is an irregular ulcer with edges undermined the base granular and bathed in thin pus The base bleeds easily on manipulation Pain is a striking feature The entire process is surrounded by edema and inflammation Patients with single lesions have a shorter period between onset and observation than do those with multiple lesions The chancroidal ulcer is both inoculable and autoinoculable

In uncircumcised individuals the ulcers appear most frequently at the edge of a phimotic prepuce or on the internal surface of the prepuce while in the circumcised male they appear on the frenum and in the coronal sulcus Because of the frequent involvement of the prepuce phimosis and paraphimosis are present Occasionally in early lesions exuberant granulations project above the surrounding skin level *ulcus molle elevatum*

In the female and on the hairy pudenda of the male small crateriform ulcers arise at the site of the follicles sometimes as many as fifty follicles being involved *follicular* or *miliary chancroid* The *dwarf form of chancroid* resembles an herpetic lesion in that it is rounded shallow and five millimeters or less in diameter The dwarf chancroid possesses sharp hemorrhagic borders and an irregular base and thus can be differentiated clinically from herpes progenitalis There is the transient chancroid *chancre mou volant* which is a small superficial ulceration 3 to 6 millimeters in diameter which involutes spontaneously without scar formation in from 4 to 6 days This evanescent character is suggestive of the primary lesion of lymphogranuloma venereum The giant and phagedenic chan

The portal of entry of the causal agent is a break in the continuity of the epithelium Men are subject to chancroid eight to ten times more frequently than women The disease runs a much milder course in women than in men and may even escape the notice of the woman The endemic areas are seaports its reservoir the prostitute This result of paramour and jollity already has gained an increase in epidemiological significance due to wide travel and diversity of interests of the millions of men engaged in global war

Pathology

Within forty eight hours after infection a small inflammatory papule appears which soon becomes a pustule[30] This pustule quickly ruptures resulting in a sharply circumscribed ulceration having inflammatory infiltrated undermined and irregular edges The epidermis shows edema of the prickle cells and papillary bodies with an infiltrate just beneath the epidermis This infiltrate is composed chiefly in the early stage of polymorphonuclear leucocytes containing Ducrey bacilli Soon a small abscess lifts up the horny layer and the corium shows dilated lymph and blood vessels surrounded by an infiltrate of polymorphonuclear leucocytes lymphocytes and a few plasma cells Necrosis with ulceration of the epidermis occurs The dense and diffuse infiltration on all sides of the ulceration is not sharply limited on its borders and continues around the vessels into seemingly normal tissue The blood vessels are the seat of a pronounced endovasculitis and perivasculitis The superficial necrosis arises from an acute perivasculitis and endovasculitis with swelling of the endothelium[31] The *H ducreyi* are more readily demonstrated in pus aspirated from the undermined edges of the ulcer than in sections of tissue

Diagnosis

Thorough investigation of a genital lesion particularly one of doubtful incubation and clinical appearance is in the initial stages of far greater importance than treatment

The clinical picture of uncomplicated chancroid is fairly typical with its short incubation period the tender painful and inflammatory character of the lesions their multiplicity and lack of induration An absolute diagnosis can be made only by demonstration of *H ducreyi* a procedure which frequently is unsuccessful

Smears — Successful smears are best accomplished by carefully syringing first the lesion with normal saline Material obtained by platinum loop is evenly distributed on a glass slide by one swift stroke of the loop content across the slide The smear may be stained by the gram method or with Wright s stain or with methyl green pyronin

a problem In its initial stage the mixed chancre has all the characteristics of chancroid but after 15 to 20 days a change in the clinical picture takes place The base of the initial lesion becomes smoother, bright red granulation tissue either partially or completely fills in the crater, and the previously irregular and undermined edges become smooth and indurated The Ducrey bacilli can be demonstrated in the early stage when the lesion resembles a chancroid while conversely the Treponema pallida are found usually in the later stage Careful clinical and serological observation for at least four months is of supreme importance to rule in or out this type of mixed infection

Etiology

The etiological role of the streptobacillus of Ducrey (*Haemophilus ducreyi*) has been established beyond doubt Greenblatt and Sanderson [8] have succeeded in isolating 20 strains in pure culture The typical organism is difficult to recognize in fresh specimens The *H ducreyi* is a slender non motile non spore bearing non acid fast gram negative short bacillus with rounded ends, arranged in pairs in groups or in parallel chains Several parallel rows of chains are characteristic in properly made smears In cultures the typical morphology of the streptobacillus appears as individual organisms in groups or in long or short chains However to culture is difficult and its value is dubious for the practicing physician

The procedure for making a successful smear consists first of carefully syringing the lesion with physiological saline solution Material then is obtained with a platinum loop and with a single swift stroke it is evenly distributed on a glass slide This procedure is less apt to rupture the chains of bacilli Methyl green pyronin is a suitable stain

The culture technic devised by Sanderson and Greenblatt [9] is as follows To tubes of beef infusion agar in slants is added 1 c c of defibrinated human blood The blood is inoculated with 0 1 c c from an actively growing culture and placed under partial oxygen tension To obtain cultures from chancroidal lesions is a difficult procedure requiring special skill To obtain the proper oxygen tension the cotton plug is cut off short and pushed slightly into the tube The upper portion of the tube is heated slightly in a Bunsen flame The tube is then sealed with a tightly fitting rubber stopper Incubation is from 2 to 3 days at 37° C During this period growth occurs in the fluid below and to a lesser extent appears on the surface of the slant

The pathogenicity of these cultures and their identity with the *Haemophilus ducreyi* found in the chancroidal ulcers have been verified beyond doubt by inoculation from culture to animal and from animal back to man Their identity was proved by successfully inoculating patients, producing typical lesions and rendering the patients capable of reacting positively to intradermal chancroid tests

associates[11] call it a striking degree of cross reactivity with other types of antigens especially when two or more genital infections are present

It is generally agreed that the skin reactivity to the Ducrey vaccine is permanent thus one must decide whether a positive reaction applies to a given genital lesion or to a previous chancroidal infection

Dmelcos Vaccine — In European clinics an antigen dmelcos vaccine is employed quite generally Dmelcos or anti Ducrey bacillus vaccine is a stabilized atoxic vaccine consisting of an emulsion of several strengths of Ducrey bacillus Each cubic centimeter contains 2 5 million of the killed streptobacilli in suspension and an antibody containing serum elaborated according to the technic of Reenstierna It is used both for diagnostic purposes and for therapy The technic for its intradermal use as a skin test for chancroid is the same as that described in the immediately preceding paragraphs Dmelcos vaccine therapy should be kept in mind for use in the occasional case of chancroid where the sulfonamides are contraindicated

Human Antigen — Cole and Levin[9] in 1935 being unable to obtain a commercial Ducrey bacillus vaccine in this country described according to the method inaugurated by Frei[15] in 1925 an antigen prepared from chancroidal bubo pus

The patient from whom the material is obtained must have a negative Frei test for lymphogranuloma venereum and the antigen must react negatively in patients with proved lymphogranuloma venereum Pus aspirated from the unruptured chancroidal bubo is diluted with five parts of physiological salt solution and heated at 60 C for two hours repeated for one hour the following day and then it is tested for sterility Using this material 0 1 c c is injected intradermally and the test read at 48 and 72 hours A positive reaction consists of an infiltrated erythematous papule with shortest diameter 5 millimeters The infiltrated area may be much larger and go on to necrosis Thus perhaps the medial surface of the thigh may be a preferable site for testing The antigen thus prepared should not be used on the same patient from which the material was obtained Cole found that five weeks after the appearance of the chancroid represents an average period required to obtain a positive reaction and he described the reaction as being specific for chancroid

Culture — The culture technic as described by Sanderson and Greenblatt[9] and previously described under Etiology is perhaps the best To make cultures from chancroidal lesions is a difficult and special procedure which preferably is attempted only under ideal conditions

Biopsy — The histology of chancroid does not present a specific or true diagnostic picture but may prove of some value in the mixed type of ulcerative lesions especially when other diagnostic measures have proved inadequate The microscopic findings are described in detail under the heading Pathology

The diagnosis by stained smear was successful in 65 per cent of cases in Greenwald's[17] hands Kornblith and associates[3] in a series of 175 cases reported that stained smears were the best single criterion of diagnosis, positive identification being attained in 88 57 per cent of their patients During this early period of search for the Ducrey bacilli at least for the first four successive days of observation repeated dark field examinations are performed to rule out early syphilis

Autoinoculation — The patient is kept at bed rest An area of skin of the abdomen is cleansed with grain alcohol permitted to air-dry and then is scarified with material from the suspicious lesion the technic being similar to that of smallpox vaccination and covered with a watch crystal At the successful inoculation site an inflammatory erythema develops within 24 hours and a pustule appears within the succeeding 24 to 48 hour period A chancroidal ulcer is revealed on removing the top of the pustule Properly prepared smears from this lesion usually reveal the streptobacilli without difficulty The former potential hazard of phagedenic ulceration resulting from this procedure is now reduced to a minimum by the use of the sulfonamide preparations

Skin Tests — A commercial antigen[11] for intradermal testing in accord with the Ito Reenstierna technic is now available The test is performed and read as is the Frei test and in this respect it is similar to the tuberculin and trichophytin reactions Using the commercial antigen 0 1 c c is injected intradermally in the mid flexor surface of the forearm or medial mid portion of the thigh The test is read within 48 to 72 hours A positive reaction is marked by an indurated papule of 6 millimeters or more in diameter The reaction generally will become positive 8 to 12 days after infection while usually it is negative up to that time

Knott and associates[11] call attention to certain definite limitations to the diagnostic value of the Ito Reenstierna test Of their cases of clinical chancroid 82 per cent gave a positive or doubtful reaction with the Ducrey vaccine but concurrently similar positive reactions were obtained in approximately 50 per cent of their patients designated as lymphogranuloma venereum syphilis or heterogeneous genital lesions other than chancroid Similarly Kornblith and co workers[3] report that 94 6 per cent of their chancroidal cases gave positive Ito Reenstierna reactions but so did 42 per cent of 64 patients with venereal disease other than chancroid In contrast Sanderson and Greenblatt[9] found the skin test to agree with the clinical diagnosis of chancroid in 96 per cent of their cases while none of the normal controls reacted positively Saunders and associates[23] found the test positive in 98 of 107 patients with chancroid while 3 of 117 apparently normal controls gave a positive reaction

Brandt and Torpin[31] believe such results to be due to parallergy or co reaction and to mixed infection among patients with venereal disease Knott and his

associates[11] call it a striking degree of cross reactivity with other types of antigens especially when two or more genital infections are present

It is generally agreed that the skin reactivity to the Ducrey vaccine is permanent thus one must decide whether a positive reaction applies to a given genital lesion or to a previous chancroidal infection

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lowing the primary lesion and serological reactions for syphilis are almost invariably positive at that time.

The fact that biological false positive serological tests for syphilis occur frequently in patients with non-syphilitic genital lesions[11,26,27,28] should be kept in mind. Also of importance is the observation[11] that when treating chancroid with a commercial Ducrey vaccine (dmelcos in this instance), although the clinical picture of syphilis is unaltered in its development, the serological and bacteriological manifestations are inhibited and delayed.

Arsenical therapy should not be started in a patient with a dark-field negative genital lesion and a low titered serological test for syphilis even if the reactivity is confirmed by a repeat test. *Quantitative tests are important in such cases.* A progressive upward trend in the reagin titer in repeated tests suggests syphilis but a constant titer at low level or a falling titer strongly suggests the possibility of a biological false reaction[11].

Lymphogranuloma Venereum.—Lymphogranuloma venereum and chancroid may be acquired at the same time. When this mixed infection is present, the diagnosis can be difficult. It is a good policy to perform a Frei test on all chancroidal lesions of long standing. Due to the life-long characteristic of a positive Frei reaction, a negative Frei test is of value regardless of whether one employs the commercial antigen[29] or the human lymphogranulomatous pus antigen.

Clinically the bubo of lymphogranuloma is slow to develop, slow to suppurate, shows little or no superficial inflammation, several lymph nodes are involved and tend to coalesce thus forming thick folds corresponding to groups of ill-defined lymph nodes. In contrast the chancroidal bubo is quick to develop, quick to suppurate, the overlying skin is acutely inflamed and the uniform rising involves only one node. The chancroidal bubo is painful and tender. The lymphogranulomatous bubo frequently is painless.

Cross-reactivity between antigens and biological false positive serological reactions for syphilis occur in chancroid, syphilis and lymphogranuloma venereum infections. Biological false positive serological reactions for syphilis in patients with lymphogranuloma venereum may disappear within 15 weeks and in patients with chancroid the serological test for syphilis may revert to negative within 2 to 5 months after the chancroid has healed. Biological false positive Frei tests in patients with early syphilis may disappear within 4 to 12 weeks after the beginning of treatment for syphilis.

Granuloma Inguinale.—The demonstration of Donovan bodies is essential to the diagnosis of granuloma inguinale. This is accomplished best by obtaining material for stained smears from deep tissue scrapings or in biopsy specimens.

The clinical appearance of a chronic persistent granulomatous process involving the groin and genital areas or elsewhere with little or no regional lymph node involvement is characteristic of the disease.

Complement Fixation — Sullivan[9] in his excellent discourse on chancroid states that Rivalier[15] succeeded in devising a complement fixation test of high specificity for chancroid. Rivalier prepared his antigen from either undiluted purified streptobacilline or crude streptobacilline which had been diluted one third, and the test was performed according to the technic of Calmette-Massol. In a group of 56 patients with chancroid 94 per cent showed a positive complement fixation test, whereas in a group of 50 patients without demonstrable chancroid the reaction was negative in 48. Positive reactions occurred as early as eight days and as late as three years after infection.

Knott and associates[11] call attention to transient false positive complement fixation tests in mixed infections of the genitalia. The complement fixation test for chancroid has not come into general use in this country, perhaps because of its difficulty of performance and because other diagnostic procedures are at least its equal in specificity.

Differential Diagnosis

Thorough investigation of a genital lesion is of the greatest importance. Although the clinical picture of chancroid is fairly typical, it should always be differentiated carefully from syphilis. The possibility of a mixed infection of these two diseases is of grave significance to the patient.

Early syphilis, lymphogranuloma venereum, granuloma inguinale, fusospirochetosis and herpes progenitalis are the chief diseases to be differentiated from chancroid. The heterogeneous entities of venereal warts, coccogenous infections, neoplasm and adenitis secondary to mycotic infection form a group of incidental diseases which usually are not confused with chancroid. Ulcus vulvae acutum occurring in virgins and others is to be considered. Should gonorrhea and early syphilis coexist, the syphilis may be greatly masked and its development delayed when penicillin is used to treat the gonorrhea.

Syphilis — If syphilis and chancroid are acquired simultaneously, the clinical course of the primary lesion will be typically chancroid for the first 14 to 21 days, following which the lesion begins to assume an indurated and erosive appearance with smooth edges and granulating base suggestive of primary syphilis.

Immediately after the patient comes under observation a dark field examination should be done, and if negative, it should be repeated on four successive days. Should the dark field studies be negative, then future investigation for syphilis should be both clinical and serological. Serological reactions for syphilis should be performed at seven-day intervals for the first six weeks, thence at fourteen day intervals until four months have elapsed subsequent to the appearance of the initial lesion.

Secondary syphilis, when it develops, usually appears within six weeks fol

tremely poor because of phimosis or paraphimosis or for surgical drainage of bubo Strenuous exercise enhances the development of bubo Alcohol and other stimulants are best avoided When exceedingly stubborn chancroid is encountered always think of some complicating infection especially syphilis On no account should an arsenical or bismuth preparation be administered unless the diagnosis of syphilis is unequivocally confirmed by dark field examination or by repeated serological tests of high titers Penicillin retards and masks the development of syphilis

Sulfonamides — The amazing and direct response of uncomplicated chancroid and of chancroid with bubo to treatment with the sulfonamides is a delight to behold The fact that the sulfonamides do not interfere with the intradermal chancroid test nor do they effect the clinical course of syphilis are obvious advantages It is possible however that during sulfonamide therapy of the acute phase of genital infections we may see transient false positive serological reactions for syphilis due either to the sulfonamide alone or to cross biological reactions

During the administration of sulfonamide drugs the possibility of toxic reactions should be kept in mind These untoward effects range from dizziness palpitation malaise mental depression nausea vomiting and anorexia through dermatitis fixed eruptions photosensitization to anemia leucopenia and renal impairment The incidence of toxic manifestations considering the relatively small amount of the sulfonamide necessary to effect recovery from chancroid must be an unusually low one

A safe procedure to follow during the first four days of a chancroidal infection even after the demonstration of *H ducreyi* is to withhold all local therapy except moist saline or boric acid dressings and to search daily by the dark field examination for *Treponema pallidum* However during this period sulfathiazole may be administered by mouth If the dark field examinations are negative at the end of four days then the lesions may be treated with soaks of 1 8 000 potassium permanganate followed by the application of sulfanilamide powder

Once the diagnosis of chancroid is established sulfathiazole is given orally for 7 days in 4 gram daily divided doses the initial dose being 2 grams

Should early syphilis be present there is no contraindication to the simultaneous use of daily full doses of mapharsen nor for that matter to the present accepted thereapy of early syphilis with penicillin

When fluctuant bubo is present it should be incised and drained Greenwald[17] using the above regimen on 73 enlisted soldiers observed no toxic phenomena from sulfathiazole and stated that all patients improved with an average of 7 6 days of time lost from duty No patient was discharged from the hospital until the lesion had epithelized completely

Hanschell[18] is credited with being the first to use sulfanilamide in the treat

Herpes Progenitalis — Herpes progenitalis is of frequent occurrence Its superficial and evanescent character relative absence of marked inflammatory change and pain and its prompt response to hygienic measures without sequelae are characteristic Only rarely does a painful, unilateral and transient bubo accompany herpes progenitalis

Fusospirochetosis Vincent s angina and trench mouth are synonymous with fusospirochetosis It is more commonly an oral infection than a genital one This disease is characterized by multiple irregular painful usually super ficial ulcerations covered with tightly adherent whitish or greenish grey slough There is an offensive putrescent odor The regional lymph nodes are enlarged Fever up to 102 F may be present Pellagra and scurvy predispose the develop-ment of vaginal and rectal lesions The spirilliform organisms are readily demon strated by dark field examination and by stained smears Vincent's treponema is a delicate organism 5 to 10 microns long actively motile and possessing 3 to 8 irregular spirals It stains gram negatively and can be cultured under anerobic conditions in serum agar and in serum broth at 37° C

Ulcus Vulvae Acutum — This form of ulcer simulates chancroid and occurs about the vulvae of virgins The commonest type is characterized by multiple small irregular shallow tender ulcerations about the introitus They may occur as a miliary eruption on the labia majora of pinhead sized lesions with slightly elevated margins and depressed purulent centers which persist only a few days New lesions appear as old ones heal The disease may last a month or more

The gangrenous types are of sudden onset and accompanied by systemic fever These painful ulcers range up to 1 5 centimeters in diameter their edges are soft and steep and the grey yellowish or bluish black surface membrane is adherent Within three to four days the membrane separates exposing a soft ulcer with a smooth floor bathed in a thin fibrinopurulent secretion Complete healing with scarring requires approximately ten days Ducrey organisms are absent Stained smears reveal multitudes of *Bacillus crassus*

Neoplasms — Cancer usually develops after the fourth decade of life The lesion develops slowly usually is nodular or indurated and there is often a history of long continued irritation In doubtful cases recourse should be had to biopsy In chronic ulcerative lesions the possibility of pseudoepitheliomatous hyperplasia simulating cancer should not be overlooked

Treatment

In the treatment of chancroid cleanliness is the first requisite Violent chemical measures the cautery and surgery today more frequently are harmful than beneficial Surgery is indicated only when drainage and exposure is ex

tremely poor because of phimosis or paraphimosis or for surgical drainage of bubo Strenuous exercise enhances the development of bubo Alcohol and other stimulants are best avoided When exceedingly stubborn chancroid is encountered always think of some complicating infection especially syphilis On no account should an arsenical or bismuth preparation be administered unless the diagnosis of syphilis is unequivocally confirmed by dark field examination or by repeated serological tests of high titers Penicillin retards and masks the development of syphilis

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Shortly after Hanschell s report Hutchison[40] Batchelor and Lees[41] Kornblith, Jacoby and Wishengrad[4] and Fox[43] reported successful results with sulfanilamide Culp[44] in 1940 collected in the literature 205 cases of chancroid treated with sulfanilamide and all but 7 of these patients were cured Noojin Callaway and Schulze[45] believe that sulfadiazine and sulfathiazole are equally effective

Combes Canizares and Landy[46] are of the opinion as based on observation and treatment of over 1 000 cases of chancroid that protracted treatment with sulfathiazole is unnecessary since the effect of the drug upon *Haemophilus ducreyi* is rapid and lethal After the lesion becomes sterile continued chemotherapy does not influence materially the healing ulcer In 97 patients with chancroid of which 17 had buboes and in 20 the chancroid was induced they administered sulfathiazole as follows 2 grams as the initial dose followed by 1 gram 4 times daily They concluded that the administration of sulfathiazole for 5 days total 21 grams in simple chancroid and for 7 days total 29 grams if buboes are present is adequate to cure chancroid Their patients were observed closely until the lesions were completely healed

Since Hanschell s original observations in 1938 reports on the use of sulfonamide preparations chiefly sulfathiazole in the treatment of chancroid are appearing constantly and the evidence seems to indicate that the drug is practically a specific for *H ducreyi* infection

Dmelcos Vaccine — The dmelcos vaccine is administered intravenously in the treatment of chancroid It acts pyrogenetically causing a transient rise of temperature to as high as 106° F the pyrexia occurring early and lasting 8 to 10 hours in most cases There apparently is no toxic effect from this severe degree of fever The hospitalized patient is given a purge and a light diet the night before injection On treatment days the patient is kept in bed and given copious fluids The first intravenous treatment is 1 c c subsequent treatments of 1 5 c c 2 c c 2 5 c c and 3 c c are given on alternate days Rarely is it necessary to give more than four injections

Using this procedure Coulter[23] in 1937 treated 37 chancroidal infections 22 of which were complicated by buboes Uncomplicated chancroids healed rapidly in several instances following the first injection In the case of complicating buboes, whether fluctuating discharging incised or not incised complete resolution was effected in all instances within 14 days In those patients with

infected dorsal slits there was a phenomenal reduction in the number of days sickness as compared with treatment excluding the sulfonamides along ordinary lines

PROPHYLAXIS

Chancroid occurs with world wide incidence The only certain prophylaxis is the avoidance of exposure wherein the disease might be contracted The local cleansing with surgical soap and water immediately following promiscuous intercourse has proved inadequate The chemical prophylaxis as recommended by the U S Army is effective in reducing the incidence of gonorrhea and syphilis but is totally inadequate in preventing chancroid This method[17] consists of (1) initial thorough cleansing of the exposed parts with green soap (2) thorough washing of the parts with 1 1 000 mercury bichloride (3) urethral injections of 5 per cent mild protein silver and (4) thorough application of ointment of mild mercurous chloride to the parts Other efforts at local chemical prophylaxis indicate that they are only partially successful

The oral use of sulfathiazole in the prophylaxis of gonorrhea and chancroid was reported first by Jose[47] in 1942 In an Asiatic Station where the incidence of chancroid was high he administered orally in divided doses 6 to 7 grams of sulfathiazole on the day following exposure Although no other chemical prophylaxis was used no case of gonorrhea or chancroid developed in this enlisted naval group

The experimental prophylaxis of chancroid has been investigated by Combes and Canizares[48] Greenblatt and Sanderson and associates[49] by Keet[50] and by others Keet administered a single 1 gram dose of sulfathiazole orally within 1 hours after intercourse in 1 80 instances and in no instance did chancroidal infection occur

Greenblatt and Sanderson and associates[49] produced experimental chancroid by inoculations with virulent strains of *H ducreyi* while Combes and Canizares[48] conducted similar experiments by autoinoculations Each investigation evaluated the prophylaxis of various chemical agents Sulfathiazole ointments were only partially successful Zephiran 2 per cent aqueous when applied to the inoculation sites within 3 hours after inoculation was an efficient prophylactic in 94 per cent of 17 cases in the Greenblatt and Sanderson group Combes and Canizares in a few cases gave sulfathiazole orally 4 hours after autoinoculation Their initial dose was 2 grams followed by 1 gram every 4 hours until a total of 5 grams were given In no instance did the autoinoculation take Later working with culture material they repeated this experiment many times with equal succes s

That possible hazards may arise from the oral use of sulfathiazole in this type of case was emphasized by Reynolds Evans and Walsh[51] They reported a

ment of chancroid To o patients he gave deep subcutaneous injections of 5 c c of 5 per cent prontosil soluble a sulfanilamide preparation followed by one or two 10 c c injections at three-day intervals In addition each patient received 3 grams of prontosil album orally in divided doses in 24 hours There was rapid and complete healing of the ulcers and a subsidence of the buboes in 5 to 10 days Circumcision and other surgical incisions healed by first intention without infection

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mild transitory impairment of visual efficiency for 24 to 48 hours following the administration of 4 grams of sulfathiazole There was no significant impairment in the performance of various psychometric tests involving fine muscular coordination The disturbance of visual efficiency particularly in depth perception, was slight but sufficient to create a potential hazard in flying personnel especially at dawn and dusk In others engaged in less risky occupations this objection to such use of sulfonamides is negligible

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CHAPTER IV

MENINGOCOCCUS INFECTIONS INCLUDING CEREBROSPINAL FEVER

By W W HERRICK

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such concern in the forces of Great Britain and the United States Even under war conditions however the continent was spared serious outbreaks

Bacteriology

The *Diplococcus intracellularis meningitidis* was first seen in the spinal fluid by Marchiafava and Celli[1] in 1884 Its cultivation and identification as a separate species was accomplished by Weichselbaum[13] in 1887 It may vary much in size It is a Gram negative organism and is stained easily by all aniline dyes including the Jenner s blood stain It is differentiated with difficulty from the gonococcus and other neisseria and may be confused with the *Micrococcus catarrhalis* *Micrococcus fla us* *Micrococcus pharyngis siccus* the *Diplococcus crassus* and *Diplococcus mucosus* In exudates the micrococcus is typically intracellular in position although it may be found extracellularly

In its growth the micrococcus is fastidious although different strains differ greatly in this respect In general animal protein such as ascitic fluid or blood serum agar with glucose bring about a more luxurious and rapid growth An atmosphere containing 10 per cent CO often aids growth of primary cultures The colonies may appear after an incubation of one or two days as transparent raised circular semiopaque objects Frequent subcultures may be necessary for identification and to maintain viability

Essential chemical constituents of the micrococcus are polysaccharides and a nucleoprotein giving cross reactions with gonococcal nucleoproteins The polysaccharides are type specific carbohydrates alike in type I and type III organisms but differing from that of type II Rake and Scherp[15] have demonstrated type specific precipitinogens in the spinal fluid of patients with meningococcic meningitis Cross precipitin reactions occur with meningococcic polysaccharides and antigonococcus and antipneumococcus type III serums

Toxins and Immunity

These are not well understood There is a true endotoxin since the bodies of meningococci upon injection into animals have toxic effects Apparently there is also a soluble toxin since cultures in broth kept long enough for autolysis to occur yield similar poisons Filtrates from agar or broth cultures of meningococci may cause severe symptoms in animals Soluble toxins thus obtained are specific for the types of meningococci concerned and are antigenic since they produce type specific antibodies when injected into animals Ferry[16] has studied these soluble toxins of

ring sporadically or in epidemics having a very variable course characterized by a primary local involvement of the upper air passages a secondary invasion of the general blood stream and a usual metastatic inflammatory process in other parts of the body

History

Although not recognized as a separate disease before 1805 many older descriptions of acute disease point to the undoubted existence of meningococcic meningitis during the middle ages when it was confounded with typhus and other fevers The first account correlating clinical and pathologic findings was made by Vieusseux[1] of Geneva who in 1805 described as "Fievre cerebrale ataxique" an epidemic of thirty three cases Following this accounts of the disease began to appear from other parts of the world

For some unknown reason the North American continent has been the home for this disease few decades having been free from epidemics of greater or less severity The first recorded American epidemic was at Medfield Massachusetts in 1806 of which a vivid description given quite independently of the work of Vieusseux[1] has been left by Danielson and Mann North[3] of New York published in 1811 the earliest monograph on the subject The contribution of the Massachusetts physicians Welsh Jackson and Warren[4] in 1813 is noteworthy During the Civil War the disease became widespread in the army With the release of troops at the end of the Civil War the infection was disseminated far and wide In 1893 there were extensive epidemics in New York City Maryland and Massachusetts The latter gave rise to the exhaustive contribution of Councilman Mallory and Wright[6] In the period from 1904 to 1907 New York again suffered severely In the year 1905 that city had 2 755 cases This epidemic was the occasion of Flexner's[7] epoch making contributions and was marked by the initial use in America of intraspinal serotherapy In 1912 Texas and Louisiana were visited This epidemic was studied by Sophian[8]

In the winter of 1917 and 1918 during the period of mobilization of troops in the war against the Central Powers there were extensive outbreaks of a virulent form of the disease among the new recruits In the camps of the South the infection was particularly rife

Great Britain in contrast to North America has enjoyed comparative immunity from meningococcic meningitis although there have been extensive epidemics on the continent Since 1874 no very extensive continental outbreak has occurred until the late war during which the continental armies were attacked by a type of the disease not unlike that which caused

agglutination reactions Dopter[17] named two types the meningococcus and the parameningococcus Gordon[18] described four types Subsequently it was found that a number of irregular intermediate types existed The correlation of these chief types is shown in Table I

As the members of these groups and their intermediates vary specifically in their immunological properties the problem of diagnostic and therapeutic serum manufacture is greatly complicated Effective serums must contain antibodies for the specific type of organism concerned

A Wadsworth and Kirkbride[19] have shown potency and valency of a serum are antagonistic to a certain extent In other words the use of too many different strains of meningococci as antigens in the preparation of serum diminishes its potency It is the general practice to limit the number of strains used in serum preparation to from four to six This principle and practice naturally limit the range of effectiveness of a given serum and make it important to vary the antigens employed as the strains of meningococci vary in different epidemics or in sporadic cases This demands constant vigilance on the part of the public health authorities and cooperation with practitioners in order to adjust the antibody content of serums to the requirements of separate outbreaks of the disease

Serum is prepared by the injection of horses with living organisms suspended in salt solution with which serum dextrose agar slants have been washed Daily injections are given for three days then repeated at intervals of seven days The amount of antigen is increased gradually In about three months a sufficiently potent serum will result

Of this potency there is no thoroughly satisfactory measure Excepting primates no animals are susceptible to the infection Therefore indirect methods of estimating the potency of serum must be resorted to Of greatest importance is the agglutination test If serum of an immunized horse agglutinates the meningococci injected into the animal in dilutions of from 1 1 500 to 1 5 000 it is considered sufficiently potent Other methods of estimating the potency of the serum are of doubtful or unproven value Although the agglutination test and perhaps the toxin neutralization test of Shwartzman[20] are the only recognized methods of measuring the potency of a given serum they are but a rough measure of therapeutic efficacy Until more accurate methods are devised however the agglutinin content of a serum must remain the sole practicable laboratory means of judging its suitability in a given infection All in all the only dependable test of a serum is its effect when properly administered to the infected patient

In the management of the disease therefore nothing is more important than recognition of the fact that to be effective the serum used

the meningococcus. Injected intracisternally in animals these cause symptoms not unlike those resulting from the injection of the living organisms. Injection elsewhere in the body causes no important symptoms. Such soluble toxins therefore have striking affinity for the cerebrospinal nervous tissue.

Gordon[1] has found that these meningococcus toxins can be neutralized in varying degrees by immune serums and that the ability of serums to neutralize such toxin was a measure of their therapeutic value. Shwartzman has shown that local skin reactions in rabbits appear after intracutaneous injection of bacterial filtrates provided the first injection was followed twenty four hours later by an intravenous injection of the same material. Shwartzman[37] reports filtrates of cultures of the meningococcus that were highly toxic and yet produced under conditions in which autolysis of the organisms probably occurred but slightly if at all. He believes his experiments on toxin neutralization suggest the presence of a true exotoxin.

The mechanism of immunity to the meningococcus is complex. Agglutination, phagocytosis, bacteriolysis and toxin neutralization have their share in the process. In theory an effective serum should be antibacterial and antitoxic. Many of the newer serums are claimed to have both these properties. The type specific serums produced by the inoculation of horses with the soluble toxin are protective in animals and are reported to have therapeutic efficacy in the infected human subject. In view of the generally unsatisfactory results of treatment by means of the serums developed by the inoculation of horses with living meningococci these wider studies of the immune factors involved in meningococcic infections and the suggestion of new measures of specific therapy are to be welcomed.

As first noted by Dopter[1] the meningococcus is not a homogeneous species but is separable into types which can be distinguished by specific

TABLE I

CORRELATION OF CHIEF TYPES OF MENINGOCOCCI*

Gordon and Murray	Dopter	American (Rockefeller)
Type I	Meningococcus	Parameningococcus
Type II	Parameningococcus α	Normal meningococcus
Type III	Meningococcus	Intermediate
Type IV	Parameningococcus β	Irregular

* F C D Murray[38] A System of Bacteriology in Relation to Medicine II 31 London 19 9

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Coughing spitting sneezing talking laughing are all possible means of transmission of droplet infection so also are handkerchiefs unwashed hands and rarely flie or other insects

The path of meningeal invasion is still a matter of debate Recent clinical experimental and necropsy studies would indicate that the transfer of meningococci from the nasopharynx to the meninges is by the blood stream rather than by the more direct path of the lymphatics through the cribriform plate of ethmoid bone and that the period of blood stream transport or stage of sep is is under suitable circumstances recognizable clinically and i a useful criterion of early diagnosis

Epidemiology

The disease may appear sporadically or in epidemics It is all the same disease however and merits no dual nomenclature It is a disea e of the humbler walks of life of crowding of poverty and in anitary surroundings In New York in 1904 and 1905 seventy six per cent of the cases occurred in the tenements It is a curse of the raw recru t having been fo ty five times as prevalent in the United States army during the six months from September 29 1917 to March 29 1918 as in civilian life during the same period (Vaughn [9])

While no age is exempt infection is rare after forty five The age of greatest susceptibility is from ten to twenty five but varies in different epidemics Infants and young children bear the brunt of some visitations as in New York in 1904 and 1905 The sexes are equally susceptible Infection appears to be promoted by any factor which reduces resistance A surprising number of cases of infection with this organism follow acute respiratory tract infection bronchitis pneumonia mea les The disease is most prevalent in the winter and spring a time when inclement weather tends to enforce an indoor life and when infections of the air passages are common It has been repeatedly noted that the disease springs up during or immediately following periods of cold damp cloudy or rainy weather and that a period of sunshine is followed by a decrease in the number of new cases Flack[21] observes also that during a period of clear weather carriers become free from meningococci much more rapidly than when the weather is inclement

Morbid Anatomy

Upon removal of the calvarium the ve sels of the dura may show intense congestion rarely hemorrhage but the membrane itself is generally without

must contain antibodies specific for the type of meningococci harbored by the patient, and conversely that serum lacking such antibody is inert. Herein lies the most common cause of failure of serum therapy of meningococcic infections.

It has been stated and is probably true that an individual does not harbor more than a single type of meningococcus at a given time. For practical purposes one may consider identical in type meningococci found in the upper air passages, spinal fluid, blood, skin or other tissues of the patient.

Carriers

The meningococcus leads a saprophytic existence in the upper air passages of a considerable number of individuals who constitute carriers and who, depending upon their associations, their personal habits, possibly upon the virulence of the organisms they harbor and other factors, become sources of contagion. The only known means of entrance or exit of the meningococcus are the upper air passages. These, therefore, assume great importance in the management of the disease.

Schorer[9] describes three groups of detectable carriers: (a) those who are in the incubation period of the disease, (b) casual carriers, (c) chronic carriers. Recognition of the first type is often of great value in arriving at a diagnosis of the premeningitic period, since proof seems clear that one hundred per cent of patients are nasopharyngeal hosts of the meningococcus during this stage. Isolation of these cases is an important factor in preventing the spread of the infection. The casual or secondary carrier usually is such for only a short time but may become a chronic carrier. The average length of time during which the meningococcus can be found in the nasopharynx of these secondary carriers is three to four weeks. About ninety per cent of carriers belong to this group. A small percentage may continue as carriers for twelve or even twenty months and then become free from the organism. The third or chronic carrier group is the most dangerous of all. Harboring meningococci usually in large numbers in the nasopharynx, tonsils or accessory sinuses of the nose, these individuals, innocent of their power for harm, keep alive the organism during non-epidemic periods and, when conditions of association, of atmosphere or other less well understood factors are favorable, transmit to others the infection to which they are immune. Not more than two per cent of carriers appear to belong to this group. A few of these are the so-called intermittent carriers discharging meningococci at intervals. The carriers have as a rule normal mucous membranes, but when the nasopharynx or tonsils are diseased meningococci are eradicated more slowly. A carrier may be doubly dangerous because of his personal habits

rare The lung is involved with surprising frequency Purulent bronchitis bronchopneumonia lobar pneumonia multiple or solitary abscesses dry pleurisy or empyema may be found These are not always or indeed usually of meningococcal origin The meningococcus has been repeatedly demonstrated in these lesions however Petechial hemorrhages may be seen on all serous surfaces Peritonitis has been observed once by the writer The spleen is moderately enlarged in about half the cases The kidneys may show cloudy swelling and congestion rarely more pronounced changes Hemorrhage into the adrenals has been observed repeatedly, so also has congestion of the adrenal vessels with pallor vacuolization and partial degeneration of the cells of both cortex and medulla

Clinical Features

Meningococcic infections might be conveniently divided for description into those cases with and those without meningitis A more useful division for clinical purposes is into three stages the first a local infection of the upper air passages the second a general invasion of the blood stream or stage of meningococcic sepsis the third a stage of metastatic localization usually in the meninges not infrequently in the joints eye lung pericardium skin or other regions A precise separation of these stages cannot always be made since they may merge one into another or may coexist Experience however has shown that such a division is of great practical value in the recognition and management of the disease

The First Stage

The first stage is a local involvement of the upper air passages Such patients are carriers It may be added that it is apparently only a recent carrier that develops the disease and that only a few carriers develop the active symptoms of the second or third stages Coryza conjunctivitis pharyngitis sinusitis ethmoiditis or tonsillitis of meningococcal origin may mark this stage of the infection The diagnosis depends upon the finding of meningococci locally Some of the cases of meningococcic tonsillitis exhibit in addition to moderate swelling and redness rather superficial thin grayish patches that are unlike the white and denser plugs of exudate seen in ordinary follicular tonsillitis

The incubation period of the second stage or stage of sepsis is variable but in many well authenticated instances it has been as short as two to four days Rarely the carrier period may last many days or even six or eight weeks before dispersion of organisms by the blood stream

notable changes Hemorrhages are not infrequent in the pia arachnoid their origin being in the opinion of Westenhoeffer[72], the sudden reduction of pressure in the subarachnoid space during lumbar puncture In cases dying within forty eight hours of onset or in those not infrequent ones which never develop meningitis there may be found a central nervous system entirely free from gross or minute variations from the normal In those showing the earliest evidence of meningitis there is congestion of the pia arachnoid and choroid plexus together with localized infiltrations of round and polymorphonuclear cells and erythrocytes The characteristic exudate is found beneath the arachnoid in the space formed by that membrane and the pia It is made up of polymorphonuclear leukocytes with a varying amount of fibrin meningococci erythrocytes and desquamated ependymal cell It may be thin and only slightly turbid or in thick masses with greenish sheen The distribution is variable The cortex may show linear masses of pus along the vessels or may be quite well covered more often the greatest aggregation of this exudate is at the base on the anterior surface of the pons about the fourth ventricle and between the pons and the cerebellum The sulci are invaded as are the ventricles The choroid plexus is congested often cystic and infiltrated with leukocytes The ependyma of the ventricles is swollen vacuolated and desquamating

In the chronic cases with internal hydrocephalus or block the convolutions are flattened the ventricles distended and the subarachnoid or ventricular systems may be blocked off by adhesions most commonly about the roof of the fourth ventricle at the sites of the foramina of Luschka and Majendie or at the aqueduct of Sylvius In many of these cases there is a general thickening of the pia arachnoid A purulent infiltration of the sheaths of certain cranial nerves may be found with hemorrhages into the ganglia a possible source of the herpes so commonly present

The lesions are not confined to the brain envelope There may be a purulent infiltration of the encephalon continuous with an identical process in the pia arachnoid This takes the form of perivascular foci of infiltration rich in pus cells red blood corpuscles and meningococci In some cases circumscribed hemorrhagic or hemorrhagicopurulent foci suggesting embolism or thrombosis are found throughout the hemispheres and in the cerebellum and basal ganglia While as a rule minute such foci may attain a diameter of two centimeters

The spinal cord shows changes not unlike those found in the brain There may be purulent infiltration of all coats and structures of the eye The accessory nasal sinuses may show empyema the exudate containing meningococci The tonsils or retrotonsillar spaces may exhibit a similar condition Otitis media or parotitis may be found

The pericardium is often the seat of inflammation Endocarditis is

tare The lung is involved with surprising frequency Purulent bronchitis bronchopneumonia lobar pneumonia multiple or solitary abscesses dry pleurisy or empyema may be found These are not always or indeed usually of meningococcal origin The meningococcus has been repeatedly demonstrated in these lesions however Petechial hemorrhages may be seen on all serous surfaces Peritonitis has been observed once by the writer The spleen is moderately enlarged in about half the cases The kidneys may show cloudy swelling and congestion rarely more pronounced changes Hemorrhage into the adrenals has been observed repeatedly so also has congestion of the adrenal vessels with pallor vacuolization and partial degeneration of the cells of both cortex and medulla

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The incubation period of the second stage or stage of sepsis is variable but in many well authenticated instances it has been as short as two to four days Rarely the carrier period may last many days or even six or eight weeks before dispersion of organisms by the blood stream

The Second Stage or Stage of Meningococcic Sepsis

In the presence of an epidemic where there exists well organized cooperation between practicing and hospital physicians or, in military organizations between regimental and hospital surgeons it is possible for an experienced personnel to recognize this stage of meningococcic infection in a very considerable proportion of cases, to thus anticipate the usual meningeal complication and to institute specific treatment twenty four to forty eight hours earlier than is the case when the meningeal involvement and the symptoms arising therefrom are made the sole criteria of diagnosis

This second stage of the infection or stage of meningococcic sepsis may have the following features The upper respiratory tract infection already described is very frequent A characteristic attitude manner and facies merit detailed description The patient is dull apathetic indifferent he prefers to be let alone resents interference and is generally plaintive in his protests at disturbance The face is expressionless the look vacant and far away He uses the least possible amount of energy in response to questioning replying usually in monosyllables and in a monotonous unmodulated voice without bringing into play the muscles of expression and relapses immediately into silence and immobility The distinct change in personality at once attracts the notice of the family physician Rarely there is active delirium or a coma from which the patient can be roused but into which he sinks again when stimulation ceases The patient lies on the side with the head bent forward and knees drawn up shielding the head with the bed clothes He is intolerant of cold A peculiar cyanosis or an ashen pallor of the face and ears is frequent The veins of the fore head are full and stand out prominently The oral secretions are peculiarly dry and viscid

The temperature is rarely over 102° in over 300 cases it averaged 101° It may be subnormal The pulse is rapid and there may be one or more slight chills but never rigor The patients almost invariably complain of being sore all over ' and arthralgia or acute polyarthritis is not infrequent These features explain in part at least the striking avoidance of spontaneou movement The deep reflexes are exaggerated with a tendency to inequality of corresponding reflexes on the left and right sides of the body There is hyperesthesia Tache cerebrale is often present but is not distinctive In some epidemics at least seventy per cent of the cases show the rash, typically hemorrhagic in character (Fig 1) Small punctate hemorrhages varying in size from a barely visible pin point to areas one centimeter in diameter appear about the shoulder or pelvic girdle the elbows or other regions subject to pressure less often on the remaining parts of the trunk the extremities face or the conjunctiva and oral mucosa These spots are

very irregular in shape and come out in crops often with such startling rapidity that within an hour the patient may become generally dotted with these purplish subcutaneous extravasations They do not disappear on pressure but fade within forty eight hours leaving a rusty fawn colored stain which may be present three or four days longer Similar spots may be found at autopsy on all serous surfaces Section shows them to be *merely capillary hemorrhages into the dermis without associated inflammatory reaction* Meningococci have been demonstrated in these lesions by Netter[1] Blanchier[2] and others The damage to capillaries resulting from constriction of a part of the body by a tight band may serve to bring out

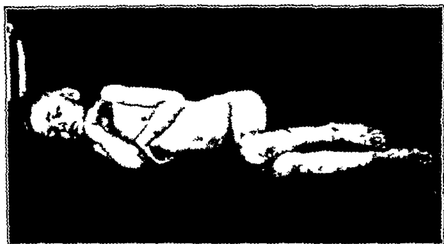


Fig 1—Characteristic attitude facies and hemorrhagic rash of meningococcic affection (Published by permission of the Surgeon General of the U S Army)

this eruption in cases in which it is not obvious In the presence of an epidemic this rash is almost diagnostic and is quite as typical as the skin manifestations of the exanthemata A few cases may show diffuse purpura *large areas of the body surface being covered by broad subcutaneous extravasations* Such are not found in the viscera or serous membranes They characterize the most severe cases in which speedy death occurs In some epidemics a small percentage of patients show a maculo papular type of eruption not unlike that characterizing typhoid fever The individual roseolous spot however is somewhat larger In some cases these *have been so numerous as to suggest an early chicken pox* *Erythematous* rashes have been noted but are infrequent and unimportant Bleb formation may complicate the hemorrhagic rashes and has been followed by gangrene

of the dermis which has involved the deeper tissues even the muscles with resulting slight or extensive scarring

A leukocytosis varying from fifteen to sixty thousand with a polymorphonuclear percentage averaging ninety is the most consistent laboratory feature of this disease Excepting lobar pneumonia no other acute infection is accompanied by such early and profound leukocytic reaction

Meningeal symptoms and signs are usually absent in this stage There may be headache and vomiting but stiffness of the neck and Kernig s and Brudzinski s signs are infrequent The spinal fluid is water clear and may or may not be under increased pressure It contains a normal number of cells usually no globulin and not infrequently isolated extracellular diplococci The readiest bacteriologic confirmation at this time is that obtained from the nasopharynx or from the blood stream The duration of this stage of sepsis is in the average case about forty eight hours it may be shorter or may be prolonged over a period of many weeks These cases with prolonged premeningitic stage are examples of the so called meningitis tarda ' In one of the writer s cases meningococci were recovered from the blood six weeks before meningitis developed

The second stage of the disease is followed by and merges with the third or stage of metastatic foci of infection This focus is meningeal in probably ninety per cent of the cases Foci are also frequent in the joints eye pericardium endocardium lungs epididymis skin pleura or elsewhere Exceptionally the meningeal involvement may declare itself at the outset

The Third or Metastatic Stage

Five types of the disease may be described the abortive the ordinary the severe the fulminating and the atypical

The Abortive Types

These are mild systemic disturbances without a local focus of suppuration Some of these patients have symptoms and signs of meningeal irritation They may present themselves with headache and vomiting may show a stiff neck, a positive Kernig s sign and increased reflexes slight fever and evidence of infection of the upper respiratory tract They do not have the rash The cerebrospinal fluid may be under increased pressure but rarely shows abnormal elements Exceptionally globulin increase and slight pleocytosis are observed with or without a few extracellular meningococci The diagnosis depends on the clinical picture and the demonstration of the meningococcus in the upper respiratory tract, cerebrospinal fluid or blood stream The blood may show agglutinins Within forty eight

hours most of these patients are convalescent. The importance of this type of the disease is largely epidemiologic. Doubtless in an epidemic many of these abortive cases are undiscovered, being passed over as harmless infections of the upper respiratory tract or other regions. They are therefore a great menace to susceptible contacts and prove the importance of careful study of every case showing fever and any minor disturbances during the presence of an epidemic.

The Ordinary Type

In this type the symptoms of the generalized infection usually last from thirty six to seventy two hours. They are mild as a rule. When present the rash is not marked and may be petechial or macular, never diffusely purpuric. The evidence of meningitis develops gradually or rapidly, unconsciousness is rare, and the course may be prolonged. The meninges bear the brunt of the infection in this, the classical form of the disease. While meningitis may declare itself at the outset, there is usually the period of a mild or moderately severe systemic disturbance which is followed by classical symptoms.

Among the possible inaugural symptoms of meningitis are: frontal headache often described as bursting, vomiting that is not always projectile, nausea, chills, delirium, convulsions, coma, arthritis, coryza, tonsillitis, pneumonia, bronchitis, eruptions.

Fever.—There is no definite type of fever. The course of the temperature is usually irregular, presenting quotidian or tertian rises to 103° or more with intervening remissions. A continuous type of fever may rarely be observed. Often there are afebrile periods of hours or days followed by rises of temperature, perhaps with chills. Some of these paroxysms suggest malaria but are of much longer duration. It is stated that a severe infection may run its course without a rise of temperature. The fever usually declines by lysis from the fifth to the seventh day. With serum treatment there may be a critical fall to normal or subnormal which is usually followed by a moderate rise with a gradual lysis later. Prolongation of fever beyond the seventh day should arouse suspicion that specific treatment is insufficient, that a secondary complication exists, or that serum sickness has appeared.

The Pulse.—The pulse rate is rapid during the stage of sepsis, but with the increased intracranial pressure of the meningitic stage it frequently becomes relatively slow and presents vagal irregularities. The blood pressure is considered in a later paragraph.

Respiration.—The respiration is rapid in the earlier phases but with the establishment of heightened intracranial pressure it may become relatively

slow and often of the Cheyne Stokes Biot or undulatory type as described by Conner and Stillman [6] According to Heiman and Feldstein [7], Cheyne Stokes respiration in children is strongly suggestive of meningitis

Sensory Disturbances —The general soreness and aching of onset may continue Pains in the back are frequent and there is great sensitiveness to cold Photophobia is not common but a general hyperesthesia is often observed The special senses of taste and of smell are often less than normally keen while vision and touch are not affected in an equivalent degree

Motor Disturbances —Convulsions are rare in the adult more frequent in childhood and often mark the cases developing hydrocephalus Athetoid movements accompanied an extensive subdural hemorrhage occurring in one of the writer cases Status epilepticus and a kind of tetany are described Carphologia and subsultus tendinum may occur A contraction of the facial muscles resulting in a moderate trismus or risus sardonicus may be seen but only at a late stage The set features the lack of play of the muscles of expression and the vacant look at once attract the eye of the practised observer

The Mental State —The striking apathy of the premeningitic stage may continue or there may develop active and spontaneous protest against the severe headache and general misery of the meningitic phase Insomnia may be a feature Delirium may be active but is exceptional and is well controlled by morphin Patients in coma can almost always be roused and usually answer intelligently Sudden death may occur soon after onset as an apparent result of overwhelming toxemia of acute hydrocephalus or in some instances from apparent increase in the bulk of the cranial contents consequent upon hyperemia and inflammatory swelling Many convalescents lack initiative and self confidence complain of headache pains and weakness are intolerant of sunlight may have poor memories and even some confusion Often months elapse before they become fit to resume work In general the outlook in such post infective disturbances in meningitis is favorable Lasting mental symptoms are much less frequent than one is led to believe from the older descriptions of the disease In the latter there is unquestioned confusion with polioencephalitis and other disorders in which deviations of mentality may be permanent

The Eyes —In the early stages the pupils are equal and uniformly dilated later irregularities may develop Hippus is common and strabismus frequent The latter is not of the paralytic type in most cases but varies from time to time The sixth nerve is most often involved because of its long and exposed course beneath the pons where it may be embedded in a mass of exudate The third and fourth nerves are not rarely implicated The prognosis of ocular palsies is good The fundus may show fullness of the veins and slight blurring of the edges of the disc With internal hydro

cephalus papilledema is not frequent. Retinal hemorrhages may occur but these are a late feature and, unlike similar lesions seen in general streptococcic infection, are not a part of the hemorrhagic extravasations of the stage of sepsis. Blindness of central origin may occur and is fortunately transitory in many instances.



Fig. 2.—Retraction of the head and the herpes of the later stages of the disease. (Published by permission of the Surgeon General of the U. S. Army.)

The Skin.—In addition to the rashes described, herpes (Fig. 2) is present in about seventy to eighty per cent, usually about the mouth but occasionally on the forehead, ear, chest, oral mucosa, tongue, extremities or genitalia. Some of the most extreme examples of facial herpes attend

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The greatest proportion of positive blood cultures is achieved in the premeningitic stage of meningococcic sepsis and before serum has been administered Positive cultures are rare after even a single large intravenous *administration of serum and are by no means the rule after meningeal* foci of suppuration have become established Certain prolonged cases resistant to serum may show meningococci in the circulating blood for many weeks despite intensive serotherapy Death is to be expected in such cases and endocarditis is often but not always present

Visceral Symptoms—These are rare Except for the initial vomiting the gastrointestinal tract is unscathed One of the writer s cases exhibited acute hemorrhagic pancreatitis and duodenitis

Genito Urinary System—The genito urinary tract seldom exhibits changes of significance except the epididymitis which is common in some epidemics This is a late complication and is not serious Latham[20] has discussed this complication in detail Retention of urine may occur shortly after onset and is often overlooked It is rare after the second or third day even in the most serious cases and may give place to incontinence Albuminuria is less common than in many other fevers Hematuria has not been observed by the writer even in cases with purpura nor has a true acute nephritis During convalescence one may rarely see a syndrome not unlike that of diabetes insipidus This may be due to disturbance of the pituitary gland by inflammatory exudate and in our experience has not been permanent The condition seems analogous to the diabetes insipidus of syphilitic basilar meningitis

Respiratory Tract—The lung complications are a chapter in themselves Bronchitis is common at the onset A more or less frank lobar pneumonia may be an initial symptom or may appear later Bronchopneumonia is surprisingly frequent in the severe cases and is a serious complication Solitary or multiple lung abscesses pleurisy and empyema have been observed There is nothing peculiar in the symptoms or pathology of these lung lesions Some of them are apparently due to the meningococcus others to secondary invading organisms The meningococcus may appear in infections of the respiratory tract as a secondary invader and without being dispersed more widely throughout the body

The Severe Type

After the usual prodromal period there is a stormy onset with marked systemic disturbance chill a fever perhaps reaching 103 great prostration or wild delirium cyanotic pallor and abundant rash The evolution of the disease is rapid and the third or metastatic stage may be reached within even twenty four hours of onset Exceptionally the premeningitic

this disease More than one third of the face may be covered Unlike the lesion of herpes zoster the vesicles complicating meningitis give rise to little discomfort Herpes is rare before the fifth day and is in consequence of little value in early diagnosis It seldom results in scarring

The Reflexes —In a few of the comatose cases the deep reflexes are abolished In general however they are exaggerated The frequently noted unequal activity of corresponding reflexes on both sides of the body finds its probable cause in the focal lesions in the central nervous system Kernig s sign while present in a majority of the cases with meningitis is not of great value in differential diagnosis since it is common in meningismus and occasional in other acute diseases not involving the meninges Brudzinski neck sign is of greater value When it is attempted to forcibly flex the head on the trunk there is an instant flexion of the thighs on the trunk and of the legs on the thighs Of somewhat less weight is Brudzinski s leg sign Upon passive flexion of the leg at the knee there is either flexion of the opposite knee (identical contralateral reflex) or extension of the opposite knee (reciprocal contralateral reflex) Babinski s reflex is rarely found early but is to be looked for in prolonged cases and is most common in those developing internal hydrocephalus Stiffness of the neck is an early and most important physical sign Great care should be exercised in estimating it and account taken not only of resistance to flexion and extension but also to rotation In meningitis there is usually restriction of movement in all directions Manipulation of the head and neck is often attended by pain and dilatation of the pupils may occur when flexion is attempted Retraction of the head and opisthotonos common in children are much less frequent in adults and are symptoms of the later stages of the disease or of basal meningitis In infants the fontanelles are bulging and the sutures may show some separation in the early phases or if hydrocephalus develops Macewen has described a tympanitic percussion note elicited over the skull when the ventricles are distended with fluid and considers this of value in the diagnosis of hydrocephalus

The Blood —With the onset of symptoms there is a leukocytic increase of from 15 000 to 60 000 with a polymorphonuclear percentage averaging ninety This has great value in diagnosis As pointed out by Stone[8] a decline in the number of leukocytes in the later stages of the disease is a favorable omen Meningococci have been seen in the leukocytes of the ordinary stained blood film Specific agglutinins are too rarely demonstrable for clinical reliance Complement binding and bacteriotropic substances may also be demonstrable Meningococci may be found in cultures from the blood in from twenty to eighty per cent of cases depending upon the stage of the disease at which the attempt is made and the method employed An excellent method is described by Baeslack[9]



Fig 3—Diffuse purpura of Meningococcus Sepsis (painted by Private D L Lake)
[illegible]

period is prolonged and marked by mild symptoms while the meningitic phase is severe The blood culture is generally positive and early diagnosis is possible

The Fulminating Type

These cases are most tragic The patient is struck down by an overwhelming toxemia he has a subnormal temperature or one of 104° or 106° and may die with appalling suddenness within even a few hours of onset rarely surviving forty eight hours The skin lesions are predominant Large and small subcutaneous extravasations often extensive and diffuse purpura (Fig 3) transform the patients startlingly There is usually no meningitis either clinically or at necropsy The blood culture is practically always positive Purpura fulminans or Henoch s purpura may be simulated Differentiation from the hemorrhagic types of the exanthemata may be possible only on epidemiologic and bacteriologic grounds

Atypical Types

The meningococcus not infrequently invades its host and leaves the meninges unscathed Instead of typical meningococcic sepsis with the expected meningeal complication one may see an acute or subacute poly arthritis with septic symptoms and a meningococcemia Certain of the arthritic purpuras doubtless belong in this category Pneumonia pe i carditis endocarditis empyema all without meningitis may rarely be caused by the meningococcus The diagnosis in these cases depends almost entirely upon bacteriologic evidence although many of the features of the premeningitic phase already detailed may be present

Relapsing Cases

It is difficult to draw a distinction between recrudescences and relapse The former occur in perhaps twenty per cent of cases If the criterion of relapse is made an arbitrary period of six weeks during which there is freedom from active symptoms relapses occurred in but one and five tenths per cent of the writer s 340 cases Other authors state that about five per cent of all cases relapse In the view of Flexner relapses are due to the persistence of meningococci in regions inaccessible to treatment The slow absorption of the meningococcic exudate revealed by necropsy study lends support to this opinion

Relapses seem to occur in cases that have had severe infections but which have responded to thorough serum treatment These repeated attacks may therefore be one of the penalties of immunity passively ac



Fi 3—D ffı e purp ra of M nmgococcus Sep (pa ıt d by Private D I Lak)
P bl I d b p f th S g G l f U L S 1 my

quired a conception which suggests the value of vaccines during convalescence which by the induction of a certain degree of active immunity might tend to forestall recurrences Infection with a type of meningococcus differing from that causing the earlier attack is possible but improbable Relapses may take place after intervals of months and there may be several attacks within a year The prognosis is generally good and most repeated attacks are less severe than the initial visitation

Meningococcus Septicemia

Of sufficient frequency to merit consideration in the diagnosis of fevers is a certain type of *meningococcic sepsis* This is marked by a prolonged and most irregular fever usually of the intermittent type with occasional chills a *polymorphonuclear leucocytosis splenic tumor* and a *characteristic rash* The skin lesion is a papule rose red in color much larger than the roseola of typhoid fever but otherwise identical These are scattered sparsely over the torso or extremities and may appear as successive individual lesions or in crops In some hemorrhagic rashes are seen The blood culture is positive Endocarditis is rare Arthralgia or arthritis are common The diagnosis of purpura rheumatica often is made in cases of this kind The course is prolonged Rarely the meninges may be involved after weeks or months of illness Generally however they are not concerned In differential diagnosis of typhoid relapsing fever malaria measles chicken pox and other infections meningococcemia must be considered

While the recognition of this type of the infection depends largely upon the bacteriologic evidence many of the features of the premeningitic phase of the more usual manifestations of the disease are to be looked for

COMPLICATIONS

The Eye

Purulent conjunctivitis with abundant meningococci in the exudate may be an early feature Superficially it resembles gonococcic conjunctivitis but is less painful does not ordinarily invade the cornea destructively and responds promptly to treatment Corneal ulceration has been observed One of the most important sequels is *panophthalmitis* which may occur in from 2 to 5 per cent of cases This accompanies the grave types of the disease and usually declares itself within the first five days of onset While in most instances but one eye is attacked both may be involved Prog

nosis as to vision is hopeless Sympathetic ophthalmia never occurs but the damaged eye is a source of pain irritation and toxemia and usually is best enucleated after a lapse of a number of weeks to permit walling off of the focus Amaurosis of central origin not uncommonly is observed in cases developing hydrocephalus or rarely in the absence of this complication In the latter event edema or an encephalitis is the probable cause and vision not infrequently is restored Slight swelling or congestion and edema of the optic nerve head may be observed Advanced optic neuritis or atrophy is rare

The Ear

Otitis media of meningococcal or other origin is not infrequent and must be carefully weighed in the diagnosis The eighth nerve is all too frequently involved in the purulent process extending from the meninges the labyrinth may be invaded and the structures of the inner ear destroyed Deafness in this case is complete and permanent If the process has not gone too far there is exceptionally some improvement Transitory deafness may be due to edema or focal lesions in the auditory center or paths A considerable proportion of convalescents show temporary impairment of function of the internal ear in lack of normal response to equilibration tests Deaf mutism may follow destruction of hearing at an early age before speech is established

The Heart

Myocarditis is rare A few patients have tachycardia and dyspnea on exertion during convalescence but actual physical signs of myocardial degeneration are almost never seen Pericarditis was present in 12 of the writer s 340 cases This may be dry and fibrinous or purulent in type and should be looked for carefully as the types with exudate are amenable to local serum treatment Endocarditis should be sought as a cause of persistent symptoms during convalescence dilatation of the heart with the development of murmurs and a positive blood culture attracting one to this possibility The prognosis is a hopeless one The blood pressure is low during the septicemic stage in serious types of infection and this finding lends gravity to the prognosis With the onset of meningitis the arterial tension usually rises somewhat and in the experience of Fairley and Stewart[11] cases in which this exceeds 120 millimeters of mercury are more fatal than those not reaching this figure In cases with internal hydrocephalus the blood pressure usually is elevated With the release of cerebrospinal fluid it may either fall or rise but as Sophian[8] has shown a fall of blood pressure

usually follows the intraspinal administration of serum and may be used as a non essential refinement in indicating when it is desirable to discontinue the treatment

Arthritis

Three types of arthritis may be observed in meningococcic infection The first is an acute polyarthritis which may be the inaugural symptom or one of the symptoms of onset It resembles acute rheumatic fever in its involvement of symmetrical joints usually the wrists knees ankles elbows or the small joints of the hand in its local pain tenderness redness and slight swelling Its pathological ba is undoubtedly is hemorrhage into the synoviae since it accompanies cases with the hemorrhagic rash and is concurrent with this lesion Usually it is transitory but lends gravity to the prognosis

The second type of arthritis is quite different It occurs late usually after the fifth day It is monoarticular usually affecting the knee joint and is characterized by great swelling but little redness and little tenderness or pain even on manipulation The copious exudate is seropurulent in character often hemorrhagic and contains demonstrable meningococci in about one half of the cases The duration of this arthritis is comparatively long but the prognosis is good

The third type of arthritis which may be observed seven or more days after the beginning of serotherapy is the serum arthritis which needs no special description

Internal Hydrocephalus Subarachnoid Block

The ventricular system and subarachnoid spaces form a series of channels through which the cerebrospinal fluid circulates from its principal point of origin in the choroid plexus to its principal point of absorption in the great venous sinuses This system of channels may be blocked by exudate in any one of a number of places Most commonly the obstruction is found about the roof of the fourth ventricle encroaching upon the foramina of Majendie and Luschka Next in order of frequency the aqueduct of Sylvius is occluded Inflammatory thickening of the pia arachnoid as a whole is a possible cause of block from interference with the general field of absorption of the cerebrospinal fluid and a hypersecretion of cerebrospinal fluid is a possible factor Fairley and Stewart[11] suggest that cerebral hyperemia and consequent increase in bulk of the cranial contents is a cause of the more acute cases with sudden death early in the course of the

disease One example of cord block has been observed by the writer The result of block is a mechanical interference with the circulation and absorption of the cerebrospinal fluid with consequent heightened intracranial pressure and a striking series of pathological changes in the brain and alterations in the clinical picture The ventricles are dilated the convolutions flattened and masses of thick fibrinopurulent exudate may be found at the sites mentioned

Internal hydrocephalus may be acute or chronic In the acute cases there is a liability to sudden death and at necropsy the bulb and cerebellum are found wedged tightly into the foramen magnum a ring of compressed brain tissue giving striking proof of great intracranial pressure Block is always to be suspected when none or only a few drops of cerebrospinal fluid can be obtained upon lumbar puncture when the fluid is very thick and when there are in addition clouded mentality increased muscular rigidity enhanced reflex activity neck stiffness opisthotonos and other evidence of marked meningeal irritation strabismus Babinski s phenomenon or at times retinal edema and vein swelling and when pronounced trophic changes occur Probably in no other condition is emaciation so rapid Bedsores are common If the obstruction is not relieved spontaneously or by *surgical measures death is certain In chronic cases this may be delayed* for several months the patient approximating the condition of a decerebrate animal

Cerebrospinal Fluid

Lumbar puncture is best performed at the fourth lumbar interspace which is on a level with a line drawn between the iliac crests The third or fifth spaces may be chosen Forcible restraint of a patient during lumbar puncture is inadvisable The exhaustion resulting from the struggles of an unwilling or terrified subject can always be avoided by adequate doses of morphin or by a light chloroform anesthesia The anesthetization of the skin with ½ per cent novocain solution is desirable Every aseptic precaution must be observed as staphylococci from the skin have too frequently caused fatal staphylococcus meningitis The fluid must never be allowed to gush out but should escape drop by drop under the control of *the stylet If clear not more than 8 c c* should be removed for diagnosis if cloudy as much as will escape readily may be allowed to flow out until the rate of flow is one drop every two or three seconds In the stage of sepsis the spinal fluid may be altogether *normal With the progress* of the disease meningeal invasion is marked by the appearance of isolated meningococci which may vary from the ordinary in form size and intensity of stain

ing later pressure and globulin may increase Sugar is diminished or absent

Pleocytosis is a later event Many of the cells may be mononuclear at first but rapidly polymorphonuclears predominate until they constitute from 80 to 100 per cent With a fully developed meningococcic meningitis the cerebrospinal fluid is thick with pus cells has a greenish sheen and on standing shows a heavy precipitate with cloudy supernatant fluid often with fibrin floccules floating in it *Meningococci ordinarily are found in the early stages At first many organisms are extracellular but as the* disease progresses and especially if specific serum treatment has been used they are found in the traditional intracellular position Rarely a cerebro spinal fluid is seen in which the cellular reaction is minimal and the clouding due to myriads of meningococci Such cases are rapidly fatal In general however organisms are few and the presence of unusual numbers argues for some other form of meningitis Albumin is much increased and may amount to two or three grams per liter Occasionally the fluid is very thick so that it escapes from the lumen of the needle with difficulty and may *coagulate spontaneously upon standing rarely it contains blood When* uniformly mingled with the cerebrospinal fluid the origin of this blood probably is the rupture of a vein into the subarachnoid space a possible consequence of too sudden reduction of pressure at lumbar puncture Traces of blood or even large amounts appearing in the first portion of the fluid escaping from the needle result from local injury to one of the veins about the cauda and rarely are serious Dry taps may result from block from plugging of the needle by too thick exudate or without assignable reason In this event the physician should make certain of the position of *the point within the arachnoid space by introducing the second needle in* another intervertebral space and irrigating through both needles with normal saline solution

With the subsidence of the infection the cerebrospinal fluid becomes clearer contains less protein fewer cells a larger proportion of which are lymphocytes fewer or no organisms and glucose returns tending to be come normal in amount Within a week or ten days in the average case the fluid becomes normal In some of the prolonged cases the fluid may *be increased greatly in amount may be almost or quite clear and may show from 500 to 1000 cells rarely with organisms*

The meningococcus is grown easily from the cerebrospinal fluid shortly after the onset of meningitis but after the inception of serum treatment attempts at cultivation generally meet with failure Not infrequently growth occurs in the undiluted cerebrospinal fluid after incubation of from three to five days

Diagnosis

Meningitis may exist concurrently with other acute infections In military hospitals one not infrequently sees meningococcic infection superimposed upon pneumonia measles influenza or mumps In these cases the clinical picture naturally is confusing and lumbar puncture the chief resource in diagnosis Where cases may be seen with the onset of any symptoms however slight the premeningitic stage may be recognized by the slight fever a somewhat peculiar attitude manner and facies the cyanosis or leaden pallor the characteristic rashes the marked leukocytosis with polymorphonuclear increase the heightened and ill balanced reflex activity the general soreness and aching or arthritis the presence of upper respiratory tract infections and the finding of meningococci in the nasopharynx by blood culture in rare instances in the leukocytes by direct examination of the stained blood film or by careful scrutiny of the thoroughly centrifugated cerebrospinal fluid Repetition of lumbar puncture at intervals of two or three hours may serve to bring the meningococci down from the upper cerebrospinal spaces which they apparently invade first and thus confirm the diagnosis at an early period With the onset of definite meningitic symptoms the diagnosis rarely presents great difficulty as in this stage lumbar puncture gives quite definite evidence While meningococci are not always found in the cerebrospinal fluid of the first puncture clinical evidence of meningitis with cloudy cerebrospinal fluid justifies prompt antimeningococcal serum therapy

Differential Diagnosis

Meningismus — In infants and occasionally in adults certain acute diseases such as scarlet fever pneumonia influenza mumps gastroenteritis and tonsillitis which seldom give rise to purulent meningitis may be attended by symptoms of meningeal irritation Organisms are seldom found and the cells rarely number more than 50 per cubic millimeter Usually the evidence of the associated disease becomes clear and the spinal fluid does not become purulent

Pneumonia — Repeatedly clinicians have pointed out the similarity of meningococcic and pneumococcic infections but usually there is no great difficulty in distinguishing the two One must remember however that meningococcic infection may begin with or may be added to a lobar pneumonia

Influenza — Not infrequently meningismus has been observed in influenza with increased pressure of the cerebrospinal fluid and an increase in

globulin and cells the latter rarely numbering more than 50 per cubic millimeter The diagnosis depends rather upon the absence of positive evidence of meningococcic infection than upon anything definite in the clinical picture of the so called cerebral type of influenza itself The lack of leukocytic increase in the blood and of important skin symptoms is to be mentioned Meningitis due to the *B influenzæ* is not very infrequent in children according to some it occurs in children with greater frequency than meningococcic meningitis

Typhus Fever —This disease and meningococcic meningitis doubtless were long confused and with good reason The presence of an epidemic of typhus the more consistent course the less pronounced leukocytosis with later appearance of the rashes are points of value

Typhoid Fever —Some of the subacute cases of meningococcic sepsis with maculopapular eruption strongly suggest typhoid as do in fact some of the more acute cases Most dependable in the differential recognition of typhoid are the longer prodromal period the more regular course the absence of leukocytosis the positive bacteriological or serological evidence from blood or urine the abdominal distention tenderness gurgling diarrhea and possible hemorrhages the more constant enlargement of the spleen and the more uniform unvarying picture

Sepsis —Sepsis with meningeal or cerebral metastasis may give a confusing picture This is especially true of streptococcic sepsis with punctate petechial rash The petechiae in these cases usually are smaller and more uniform in size than those seen in meningococcic infection and are found more often in the retina The findings of the blood culture and the frequent implication of the endocardium generally are distinctive of the common form of sepsis

Poliomyelitis —The cerebral form of poliomyelitis may be very difficult to differentiate from meningococcic meningitis In poliomyelitis there is often an initial gastroenteritis the temperature of onset is higher declining more promptly than in meningitis while leukocytosis is less the cerebrospinal fluid shows a higher proportion of lymphocytes the reflexes are ordinarily diminished or absent and paralysis a development Herpes and hemorrhagic eruptions are absent and delirium and pronounced meningeal irritation usually are less marked in poliomyelitis and the bacteriologic evidence is by ordinary methods negative

Tetanus —Superficially the picture may not be dissimilar from that of meningococcic meningitis but the paroxysmal character of the attacks the risus sardonicus the trismus the history of a wound the absence of headache and the lack of polymorphonuclear increase in the cerebrospinal fluid usually give decisive evidence

Diagnosis

Meningitis may exist concurrently with other acute infections In military hospitals one not infrequently sees meningococcic infection super imposed upon pneumonia measles influenza or mumps In these cases the clinical picture naturally is confusing and lumbar puncture the chief resource in diagnosis Where cases may be seen with the onset of any symptoms however slight the premeningitic stage may be recognized by the slight fever a somewhat peculiar attitude manner and facies the cyanosis or leaden pallor the characteristic rashes the marked leukocytosis with polymorphonuclear increase the heightened and ill balanced reflex activity the general soreness and aching or arthritis the presence of upper respiratory tract infections and the finding of meningococci in the nasopharynx by blood culture in rare instances in the leukocytes by direct examination of the stained blood film or by careful scrutiny of the thoroughly centrifugated cerebrospinal fluid Repetition of lumbar puncture at intervals of two or three hours may serve to bring the meningococci down from the upper cerebrospinal spaces which they apparently invade first and thus confirm the diagnosis at an early period With the onset of definite meningitic symptoms the diagnosis rarely presents great difficulty as in this stage lumbar puncture gives quite definite evidence While meningococci are not always found in the cerebrospinal fluid of the first puncture clinical evidence of meningitis with cloudy cerebrospinal fluid justifies prompt antimeningococcal serum therapy

Differential Diagnosis

Meningismus — In infants and occasionally in adults certain acute diseases such as scarlet fever pneumonia influenza mumps gastro enteritis and tonsillitis which seldom give rise to purulent meningitis may be attended by symptoms of meningeal irritation Organisms are seldom found and the cells rarely number more than 50 per cubic millimeter Usually the evidence of the associated disease becomes clear and the spinal fluid does not become purulent

Pneumonia — Repeatedly clinicians have pointed out the similarity of meningococcic and pneumococcic infections but usually there is no great difficulty in distinguishing the two One must remember however that meningococcic infection may begin with or may be added to a lobar pneumonia

Influenza — Not infrequently meningismus has been observed in influenza with increased pressure of the cerebrospinal fluid and an increase in

to 1917 inclusive it ranged from 44 to 60 per cent in the military establishments and from 65 to 68 per cent in the civilian population In the United States in 1917 the average fatality rate for 28 states was 71 9 per cent in 1935 of 5 591 cases reported in the entire United States 2 657 died a mortality of 47 5 per cent Results of treatment therefore are far from satisfactory

The most important factor is an early diagnosis When intensive treatment with suitable serum is begun within forty eight hours of the onset the mortality varies from 10 to 20 per cent If treatment is deferred beyond the second day this rate rises above 20 per cent increasing to 35 or 40 per cent in those cases not treated before the seventh day of the disease

A second factor of scarcely less importance is the availability of a proper serum one containing adequate antibody for the type of organism to be combatted A prompt response to serotherapy is a good omen

Before the third year meningococcic meningitis is highly fatal The difficulty of early diagnosis in infants and their greater liability to posterior basic meningitis with block contribute toward this result The outlook is better in cases with gradual onset When the complete picture of the disease develops within a few hours the prospects are more grave A marked petechial eruption is a serious omen diffuse purpura a death sentence The roseolar rashes indicate a mild type of the disease Pneumonia and pericarditis or an early polyarthritis justify a very guarded prognosis Cases with late monoarthritis usually recover Ptosis strabismus and other indications of definite local lesions are serious Subarachnoid block is one of the gravest complications and unless relieved means eventual death Failure to respond promptly to serum treatment is of ominous import

The remote progno is of ocular palsies and other lesions arising from implication of the cranial nerves is good excepting deafness The consequences of involvement of the eighth nerve usually are permanent Permanent mental defects are extremely rare but do occur Deaf mutism may follow destruction of hearing at an early age Various grades of mental enfeeblement may result from the hydrocephalus or encephalitis which may complicate the disease

There are not sufficient facts bearing upon the relative virulence of the several types of meningococci to influence greatly prognosis According to Drought and Kennedy[37] the English Type II the normal or regular type of the French classification offers the most favorable outlook while the mortality from the English Type III a French and American intermediary type is higher The highest mortality 60 per cent was noted in infection with the English Type I the parameningococcus of Dopter

Tuberculous Meningitis — A family or personal history of tuberculosis and the physical signs of the pulmonary or glandular forms of the disease are of the first importance In tuberculous meningitis there is commonly a prodromal period with irritability slight fever and emaciation Skin rashes are infrequent and when present are typically papular and not hemorrhagic The leukocytes seldom are greatly increased Choroidal tubercles may be seen The cerebrospinal fluid rarely is turbid rarely contains over a few hundred cells the greater proportion of which are lymphocytes and almost always shows tubercle bacilli on careful staining and examination of the floccules of fibrin that are seldom absent

Epidemic Encephalitis — This may give a picture not unlike that of suppurative meningitis The onset is less abrupt however as a rule fever and leukocytosis are not such features and cerebral symptoms predominate Hyperesthesia is less stupor and somnolence are prominent The spinal fluid differs sharply The cells may be absent or number not more than 100 in a cubic millimeter Protein usually is normal Sugar is normal or increased Organisms are absent The course is prolonged and some of the well known sequels may appear

Suppurative Meningitis - Suppurative meningitis caused by organisms other than the meningococcus usually is secondary to some focus of infection adjacent to the meninges in the middle ear in the accessory nasal sinuses more rarely in the face or scalp exceptionally by metastasis from a more remote point In contrast to the usual findings in meningococcic meningitis organisms are abundant and the diagnosis on bacteriologic grounds seldom in doubt Thorough examination of the ears should never be omitted in the presence of meningeal symptoms

Other conditions which may be confounded with meningococcus meningitis are cerebral hemorrhage or thrombosis cerebral abscess uremia diabetic coma hysteria tetany epilepsy acute mania delirium tremens rheumatic fever

Prognosis

The path of him who would predict the duration or the outcome of this disease is beset with pitfalls The extremely irregular course the frequent relapses the numerous grave complications such as hydrocephalus pneumonia or sudden death make the experienced wary of prognostics

Since the establishment of serum treatment the reported mortality has averaged not far from 30 per cent The general mortality rate however is decidedly higher than this figure In England for example from 1914

to 1917 inclusive it ranged from 44 to 60 per cent in the military establishments and from 65 to 68 per cent in the civilian population. In the United States in 1917 the average fatality rate for 28 states was 71.9 per cent; in 1935, of 5,591 cases reported in the entire United States, 2,657 died, a mortality of 47.5 per cent. Results of treatment, therefore, are far from satisfactory.

The most important factor is an early diagnosis. When intensive treatment with suitable serum is begun within forty-eight hours of the onset, the mortality varies from 10 to 20 per cent. If treatment is deferred beyond the second day this rate rises above 20 per cent, increasing to 35 or 40 per cent in those cases not treated before the seventh day of the disease.

A second factor of scarcely less importance is the availability of a proper serum, one containing adequate antibody for the type of organism to be combatted. A prompt response to serotherapy is a good omen.

Before the third year meningococcic meningitis is highly fatal. The difficulty of early diagnosis in infants and their greater liability to posterior basic meningitis with block contribute toward this result. The outlook is better in cases with gradual onset. When the complete picture of the disease develops within a few hours the prospects are more grave. A marked petechial eruption is a serious omen; diffuse purpura, a death sentence. The roseolar rashes indicate a mild type of the disease. Pneumonia and pericarditis or an early polyarthritis justify a very guarded prognosis. Cases with late monoarthritis usually recover. Ptosis, strabismus and other indications of definite local lesions are serious. Subarachnoid block is one of the gravest complications and unless relieved means eventual death. Failure to respond promptly to serum treatment is of ominous import.

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broths or cocoa soups thickened with flour, rice or other cereal gruel, any cooked cereal, milk toast ice cream custard, junket or other simple pudding may be given Tea and coffee should be avoided as tending to increase nervous irritability In cases which tend to be prolonged a high caloric diet should be enforced, giving any simple easily digested food which the patient may take readily the caloric content being increased where possible by the addition of lactose Of the highest importance is an adequate fluid intake Almost without exception at necropsy the bodies of those dying from meningococcic infection lack the ordinary amount of fluid Patients may drink almost without limit and should be given in addition to water lemonade orangeade, imperial drink or other palatable beverages to which lactose may be added In cases that persistently refuse nourishment lavage may be resorted to best when the patient is under the influence of chloroform or morphin and in connection with the narcosis that may be required for intraspinal treatments Sufficient fluid intake may be insured by hypodermoclysis or transfusions of saline solution or of glucose in 20 per cent solution Of the latter 200 to 300 c c may be given at twenty four hour intervals It is particularly useful in the event of malnutrition

Eyes —The eyes should be shielded from strong light but otherwise left alone the physician bearing in mind always the possibility of panophthalmitis and the tendency for any trauma to bring about this complication If meningococcic conjunctivitis is present the conjunctival sac should be washed out gently every two hours with a saturated solution of boric acid, and one or two drops of a solution of 20 per cent argyrol introduced two or three times daily In the intervals a 50 per cent solution of antimeningococcic serum may be dropped into the eye with good effect Cold compres es also are useful

Mouth —The usual mouth toilet is enforced bearing in mind always the frequent presence of the meningococcus in the nose and throat The sputum and nasal discharges must be collected on paper or gauze and burned Gowns should be worn by attendants also masks made of at least three layers of rather closely woven cheesecloth The washing of hands with a 2 per cent solution of liquor cresolis compositus or equivalent antiseptic after handling the patient or his discharges is to be enforced The patient should not be released from observation without having shown three negative cultures from the nasopharynx at intervals of two days

Serum and Antitoxin Treatment

Serum —Meningococcic infection may be divided conveniently for purposes of treatment as for diagnosis into three stages

1 Local in the tonsils nasopharynx, nares and accessory sinuses or conjunctiva

2 General the invasion of the blood stream or meningococcus sepsis

3 Metastatic in the meninges in about 90 per cent of the cases with or without involvement of the joints lungs eye pericardium and other structures

These stages may overlap and merge Furthermore the short duration and the difficulty of recognition of the second stage under ordinary conditions makes it important to continue to devote the greatest attention to the meningeal involvement

The Local or Carrier Stage — Recognition of the first or carrier stage results only from culture since there is nothing specific in its clinical manifestations Its treatment is almost entirely local Dichloramin T in 0 5 or 0 25 per cent solution, is recommended as a nasal and pharyngeal spray Practically normal saline solution liquor antisepticus alkalinus or peroxid of hydrogen in 30 per cent solution gives results that appear equivalent Resistant cases may yield to undiluted antimeningococcic serum dropped into the nares when the patient is lying on the back the upper air passages having been cleaned by a preliminary spray of a normal saline solution Better results have been reported from giving sulfadiazine by mouth daily in small doses until cultures become negative Elaborate apparatus for spraying vaporizing chambers and the like probably are not worth their trouble It is to be remembered that time will cure the majority of these carriers, the meningococcus as a rule not persisting in more than 10 per cent of them for over ten days Open air and sunshine are valuable aids these together with a normal mucous membrane seem more dependable prophylactics or curatives than irritating antiseptics Approximately one per cent of the carriers will not yield to any of the methods of treatment mentioned These are doubtless cases with inaccessible foci in tonsils pharyngeal adenoid tissue or accessory nasal sinuses It may be best to deal with these foci surgically Little result is to be expected from vaccines since the chronic carrier apparently vaccinates himself continually from the site of infection

The Second Stage or Meningococcic Sepsis — Intravenou serum treatment always is a serious procedure and must not be undertaken lightly even by the experienced Without the greatest care one may sooner or later see serious and even fatal consequences from the intravenous injection of large amounts of serum whether in meningococcic infection pneumonia tetanus or other disease The time factor is all important and in the septicemic cases every hour counts and delay in treatment is not to be entertained

The Intravenous Serum Treatment[33] — Sensitization should be determined by the intracutaneous test A fraction (0 01) of a cubic centimeter of the horse serum is injected into the skin of the forearm so that a small welt is made As a control a like amount of normal saline solution is injected at the same level a short distance away If the subject is sensitive an urticarial wheal will appear

at the site of the injection of serum Within a few minutes to one hour, this raised area with whitened center and erythematous border may attain a diameter of 5 cm or more Its absence does not always rule out sensitization If the skin test is negative one injects at once from 0 5 to 1 c c of serum subcutaneously as a desensitizing dose If the skin test is positive, more caution is necessary, and 1/10 c c is injected first subcutaneously If no symptoms result, 0 5 c c is injected thirty minutes later then 5 and 10 c c at thirty minute intervals The intravenous injection of one or two drops is then tried If no immediate serum effects follow these injections one may proceed safely with the intravenous treatment with the further precautions to be described

The desensitization by serum may be aided by drugs, of which atropin is chief One half hour before an intravenous injection atropin sulphate, 0 6 to 1 2 mgm (1/100 to 1/50 grain) should be given hypodermically to an adult If there is restlessness apprehension or difficulty in controlling the patient, morphin, 10 to 15 mgm (1/6 to 1/4 grain) should also be given at this time Experience with over one thousand intravenous injections leads to the opinion that atropin should never be omitted as a preliminary to the first large intravenous injection of serum One hour after the desensitizing injection of serum in individuals giving a negative skin test or one hour after the injection of 10 c c without reaction in sensitive individuals one may proceed with the first intravenous injection The serum may be given without dilution and probably is more effective thus If the serum contains a precipitate it is to be filtered through sterile cotton The simplest apparatus for injection is a 20 c c Record or Luer syringe In adults the vein at the elbow is the most convenient site The external jugular may be used It is proper to give serum to infants by the longitudinal sinus reached through the anterior fontanel The syringe is filled with serum and the needle introduced into the vein which is distended by moderate compression above The slight withdrawal of the piston with flow of blood into the syringe indicates that the vein has been penetrated by the point of the needle A narrow strip of adhesive plaster serves to hold the needle in place The most critical part of the entire treatment then follows

The secret of safe intravenous serum injection is the slow injection of the first 15 c c The rate of injection should not exceed 1 c c per minute If the first 15 c c are introduced without serious symptoms, the rest of the injection may be made at a much more rapid rate so that the injection of 100 c c , the ordinary adult dose need not occupy more than thirty minutes During the first minutes of the injection the operator must be on the alert for immediate serum effects and upon their appearance must without delay stop the injection These symptoms in the order of their importance are dyspnea, collapse, precordial distress, great restlessness or apprehension, rapid weak or irregular pulse cold sweat vomiting

urticarial rash If the e symptoms are slight and pass off at once the injection may be renewed at the same sitting *always with the same precaution of a slow* initial rate of injection if more severe the injection should be stopped altogether and the attempt renewed after one or two hours This second attempt seldom gives trouble the patient being desensitized completely by the earlier serum ad ministration so that further injection may be made without hesitation In each and every injection however the first 15 c c should be introduced at a rate not to exceed 1 c c per minute If the symptoms of anaphylaxis do not cease imme diately when the injection is stopped adrenalin 1 to 1000 solution 0 6 to 1 c c (10 to 15 minims) should be given subcutaneously or even by vein if dyspnea or collapse is serious Artificial respiration might be necessary if re piration were greatly embarrassed or ceased If great restlessness is present morphin is helpful

In evere cases of meningococcic infection in the adult, antimeningococcic serum in doses of 100 c c should be given every eight twelve or twenty four hours until there is definite improvement or until four to six doses have been given The average case will not require more than three intravenous serum treatments

The Third Stage of Locali ation in Meninges or Elsewhere —This stage merges with the second and may exist simultaneously with it In the average ca e its treatment can hardly be considered apart from the second stage or the stage of sepsis In the majority of instances therefore the intravenous serum treatment is combined with the intraspinal In cases in which the diagnosis is made after several days illness and when the disease process has localized in the meninges intravenous treatment may not be necessary especially if desirable response to intraspinal therapy is had This is particularly true of the less serious types of infection which do not demand intensive methods

Intraspinal Serum Treatment —Lumbar puncture in meningitis has two objects first drainage second the introduction of specific antiserum according to the method of Jochmann and of Flexner and Jobling No rule which will apply to all cases can be given The number of lumbar punctures the amount of fluid removed the amount of serum administered must vary with the severity and type of infection When a well marked meningitis is present with thick purulent *spinal fluid and marked systemic disturbance drainage should be continued until* the rate of flow approximates one drop each second or two or until the patient complains of severe headache About 30 c c of serum warmed to body tempera ture should then be allowed to flow into the subarachnoid space by gravity it should never be injected forcibly The foot of the bed should be raised about ten inches for one hour following the treatment in order to promote gravitation of the serum to the upper subarachnoid spaces If a large amount of cerebros inal fluid is obtained readily by the lumbar puncture as much as 45 or even 60 c c of serum may be injected at a time during the acute phases of the disease only

Within the limits mentioned one should, in general, inject an amount of serum 5 to 10 c c less than the amount of cerebrospinal fluid withdrawn This treatment should be repeated every twelve hours until three doses have been given If the patient is not in a serious condition the interval of treatment may be made twenty four hours The number of intraspinal treatments will average four some milder cases will require only one or two injections, while more severe cases may require even ten or twelve

The intraspinal treatment may be discontinued or given at less frequent intervals according to the following indications first, a marked improvement in the general symptoms as shown by a fall in temperature, clearing of the sensorium and lessening of the signs of meningeal irritation in other words, when the patient looks better second when the cerebrospinal fluid becomes less cloudy, contains no organisms when lymphocytes reappear in numbers, and when its sugar content becomes normal

To sum up therefore the ordinary case should receive from three to four intravenous injections and an equal number of intraspinal treatments within the first forty eight hours If satisfactory effect does not result from this intensive serum treatment something is wrong

Causes of Unsatisfactory Results from Serum Treatment — The trouble may be First — an overwhelming infection In this case death is not long delayed

Second — the employment of a serum not containing antibodies specific for the strain of meningococcus affecting the patient

Third — meningococci walled off in some part of the ventricular or subarachnoid systems inaccessible to serum treatment

Fourth — other complications than meningitis

Of these causes the second is the most important Failure in the serotherapy of meningococcic infection most often is due to lack of proper serum This point cannot be emphasized too strongly A serum which is effective against one of the four great groups into which meningococci have been separated according to their specific agglutinability may give disappointing results when used against another group Every physician undertaking to treat meningococcic infections should be well aware of this fundamental fact There are two measures of the therapeutic efficacy of anti meningococcus serum first its clinical effect, second its agglutinin content

Therapeutic efficiency and agglutinin content run roughly parallel If a laboratory is available the serum employed may be tested for specific agglutinins for the organisms isolated from the cerebrospinal fluid blood or nasopharynx of the patient Agglutination should take place in dilutions of at least 1 to 400 better 1 to 800 or 1 to 1 200 If the serum does not agglutinate the organisms in a dilution of 1 to 200, it is rarely of therapeutic value Unfortunately the commercial

serums too frequently are deficient in agglutinins and often give disappointing results

In the event of unsatisfactory results from the use of a given serum and in the absence of suitable laboratory facilities for measuring agglutinin content the attending physician should immediately secure serum from another source in the hope that it will contain antibodies specific for the strain of meningococci harbored by the individual patient The addition of complement preferably in the form of fresh human blood serum from convalescents in the ratio of 5 c c to each 20 c c of antimeningococcus serum apparently increases the bacteriotropic effect of the latter and is justified by the experimental work of McKenzie and Martin and the clinical observations of Fairley and Stewart

Indications of Fx cssi c Treatment — It is possible to overdo treatment In general it is best to make a concentrated attack upon the disease at the earliest possible moment according to the method described then to cease specific therapy for twenty four hours provided meningococci have disappeared from the spinal fluid Drainage had best be continued once every twenty four hours until the spinal fluid is fairly clear and contains less than 1 500 cells per cubic millimeter If meningococci persist or reappear and systemic symptoms continue a second series of two to four intravenous and an equal number of intraspinal treatments should be given at intervals of twelve to twenty four hours according to the gravity of the symptoms

In most cases the amount of serum which can be administered by the subarachnoid route is limited If intraspinal serum administrations give great discomfort pain in the back legs or head and are followed by an increased amount of meningeal irritation one has reached the not infrequent stage of hypersensitiveness of the meninges to serum In this event no more serum should be administered intraspinally even if a few meningococci persist In these hypersensitive cases often it is wise also to discontinue drainage by lumbar puncture unless the fluid is thick and a block is feared Usually however in this condition the fluid is thin and only moderately cloudy Not infrequently such a patient will improve from the time intraspinal serum treatment is omitted and requires no further serum

From the seventh day after the inception of serum treatment serum sickness may appear This is characterized by a rise in temperature urticarial or erythematous rashes arthritis glandular swellings or edema

The use of vaccines in the early phases of convalescence with a view to forestalling recurrences by the possible development of an additional active immunity has some clinical and experimental justification and the subcutaneous injection of three doses of a half billion killed meningococci at weekly intervals may be advised

Antitoxin — As a result of the work of Ferry[36] upon the soluble toxins of the meningococcus a specific antitoxin has been developed and has had limited use in treatment Hoyne[4] claims exceptionally favorable results In a series of 31 cases treated solely by the intravenous route the mortality rate was 6 4 per cent a figure in contrast with the previous nineteen years mortality rate of 50 6 per cent Petty[11] reports an epidemic of 95 cases in Lynch, Kentucky Early diagnosis was possible and the only specific treatment used in these cases was the intravenous administration of meningococcus antitoxin The mortality rate in this group was 6 3 per cent In a group of 13 cases, not having the benefit of early diagnosis and of the same treatment the mortality was 38 4 per cent Several other recent writers speak favorably of their results in the treatment of meningococcus meningitis with antitoxin These results are so arresting that one must at least feel hopeful that this newer method of treatment represents significant progress

Hoyne[4] advises the following technique A sample of blood is obtained for culture If there is little or no rigidity of the neck, spinal puncture is omitted The specific material is given entirely by the intravenous route The initial dose is 50 000 to 100 000 units of antitoxin This is given in twice the amount of a normal saline solution to which 10 to 15 drops of epinephrine solution is added The solution is given in the vein at the rate of 60 drops a minute The treatment is repeated in twelve to twenty four hours according to the condition of the patient Thereafter if the infection is under control, lumbar puncture is performed only for the relief of intracranial pressure It is claimed that serious serum reactions have not occurred with this treatment and that fatal cases are those showing necropsy evidence of encephalitis The efficacy of intravenous therapy with antitoxin would seem to confirm the findings of Herrick made in 1917 during the epidemics of the World War namely that a great reduction in mortality rate results from early diagnosis and the intravenous administration of large amounts of specific antiserum

Chemotherapy

Sulfonamides — If meningococcal infections were as frequent as pneumococcal the results of their treatment with the sulfonamides would be hailed as a triumph quite equal to that achieved in the management of the pneumonias So successful is the new chemotherapy that previous ideas of the treatment of this infection must be revised radically Serum so long the main reliance has been largely superseded by a chemical which by its mere oral use, has given a much more effective control of the disease This is a great boon to the patient and to the physician as well The course of the disease has been shortened, its severity mitigated the complications made fewer and the mortality lessened The dan

gers of anaphylaxis and the discomforts of serum sickness are done away with There is saving of time and of expense With reason one might have an attitude of skepticism as to the general value of serum in the treatment of meningococcal infections since the indicated mortality of this disease for the country at large has been not far from 50 per cent even reaching 75 per cent in some epidemics Only in practiced hands and where special circumstances have allowed early diagnosis and prompt and expert treatment have mortality rates as low as 15 per cent been achieved With the sulfonamides these rates are seldom above 15 per cent and vary in reported epidemics from 0 to that figure

In meningococcal infections the sulfonamides may be given by the oral intravenous intramuscular or intraspinal routes From the alimentary tract muscle or blood stream these compounds penetrate the subarachnoid spaces and appear in the cerebrospinal fluid in a concentration somewhat less than that in the circulating blood In most cases this concentration is approximately one half that of the blood but is subject to great variations reaching a possible maximum of 30 mgm per 100 c c Interestingly enough the concentration of sulfonamide in the cerebrospinal fluid does not always bear a direct relation to the therapeutic effect even small dilutions often being sufficient to bring about the presumed bacteriostatic action of the drug It is of great importance however to give adequate doses of the sulfonamides especially at the beginning of treatment otherwise the offending organism may develop a resistance which defeats treatment

At the time of this writing four compounds are available These are sulfanilamide sulfapyridine sulfathiazole and sulfadiazine The choice of the particular preparation to be used is a matter of opinion to a large extent There are data to indicate that sulfathiazole penetrates the subarachnoid spaces less readily than the other compounds and therefore had best be eliminated from consideration Certain observers however notably Banks report excellent results from the use of sulfathiazole In an epidemic of 96 cases thus treated Banks reports a mortality of 2 1 per cent There can be little criticism therefore if availability toxic effects of other sulfonamides or other circumstances suggest the desirability of sulfathiazole

Sulfanilamide and sulfadiazine appear to have been equally effective in the chemotherapy of meningococcic infections Sulfadiazine however has certain advantages it is less toxic than the other sulfonamides it penetrates the cerebrospinal fluid in concentrations from 50 to 75 per cent of that in the circulating blood Furthermore less tissue damage results from this drug it maintains itself in the blood stream in higher concentrations than other sulfonamides and predominantly in the unconjugated form while its acetyl derivative is excreted readily in the urine With sulfadiazine toxic effects are rare The most frequent serious complication involves the urinary tract and is characterized by

deposit of crystals in the tubules or ureters with resultant renal failure from the obstruction to the secretion or excretion of urine. This is rare in the younger age groups that are more often victims of this infection, it can be forestalled as a rule by the administration of sufficient fluid to insure a urinary output of not less than 1,000 c.c. in twenty four hours and by rendering the urine alkaline. To attain the latter end the average adult requires from 12 to 15 grams of sodium bicarbonate daily given in suitably divided doses together with the sulfadiazine. The accompanying table (Table II) prepared by Dr. William Province of the Presbyterian Hospital, New York City, gives the experience of that institution in the relative toxicity of the sulfonamides.

TABLE II

Toxic Reactions of Sulfonamides

	Sulfanilamide 200 cases	*Sulfapyridine* 200 cases	*Sulfadiazine* 200 cases	*Sulfathiazole* 200 cases
Nausea	36	60	34	2
Vomiting	11	52	22	1.2
Crystals in urine	0	4.5	17	10
Hematuria	0	5	1.6	1
Dermatitis	2	2	8.4	3
Fever	14	3	8.9	1.2
Anemia	7.5	3.5	2.2	0
Leucopenia	0.5	0.5	0.5	0
Psychosis	4	4.5	0	0.5
Cyanosis	48	8.0	0	0

Of the toxic effects listed only hemolytic anemia, granulocytopenia, crystalluria, oliguria, notable icterus and perhaps drug fever may be judged as indications for discontinuing sulfonamide medication.

The following table (Table III) from Gregory and associates gives the accepted dosage of the sulfonamide compounds.

TABLE III

Dosage of Sulfonamides

Oral Treatment	*Initial Dose*	*Maintenance Dose*	*Intervals*
Adults (100 lbs. and over)	3.0–6.0 gm. (50–90 gr.)	1.–1.5 gm. (15–20 gr.)	4 hours
Adults (50–90 lbs.)	2.0–3.5 gm. (30–50 gr.)	0.6–1.0 gm. (10–15 gr.)	4 hours
Children (25–50 lbs.)	1.5–2.0 gm. (20–30 gr.)	0.3–0.6 gm. (5–10 gr.)	4 hours
Babies	0.6–1.5 gm. (10–20 gr.)	0.3 gm. (5 gr.)	4 hours
During convalescence			
(adults)		0.6–1.0 gm. (10–15 gr.)	4 times daily
(children)		0.3–0.6 gm. (5–10 gr.)	4 times daily
(babies)		0.3 gm. (5 gr.)	4 times daily

TABLE III (*continued*)

Intravenous or subcutaneous use

1 per cent solution of powdered sodium sulfanilamide in normal salt solution

	Initial Dose	*Maintenance Dose*	*Intervals*
Adults (100 lbs and over)	700 c c	500 c c	8 hours
Adults (50–90 lbs)	300–500 c c	200–300 c c	8 hours
Children (25–50 lbs)	100–300 c c	100–200 c c	8 hours
Babies	100 c c	100 c c	8 hours

In an infection of such gravity it is wise to adopt vigorous methods of treatment The object of chemotherapy is the attainment of a blood level of sulfonamide of from 10 to 16 mgm per 100 c c at the earliest moment and its maintenance for the duration of symptoms of the acute stage While not necessary in the average case a desirable general rule is an initial intravenous dose of the drug of choice 700 c c of a 1 per cent solution of the powdered sodium salt in normal salt solution with or without the addition of 5 per cent glucose Once the desired level of sulfonamide is attained, the usual oral method of administration is followed unless vomiting convulsions coma or other circumstances interfere Where conditions make intravenous medication difficult, the oral route may be used exclusively with confidence

Recently a newer sulfonamide has been offered This is sulfamerazine This compound is absorbed rapidly from the gastrointestinal tract and is rather slowly excreted by the kidneys According to Hageman and associates adequate blood levels can be maintained by doses at 8 hour intervals The initial dose suggested is 4 gm given orally with maintenance doses of 1 gm every 8 hours In serious ca es twice this amount may be given Crystalluria and hematuria can occur Whether these are more serious than similar complications seen at times in treatment with sulfadiazine is not yet known Other toxic manifestations are rare Sulfamerazine diffuses into the spinal fluid in concentration roughly 50 per cent of that in the blood The average concentration in the blood following the dosage advised is 13 gm in 100 c c with outside limits of 9 and 23 gm

In the limited number of cases in which it has been used sulfamerazine seems to have controlled meningococcic infections as satisfactorily as the older sulfonamide compounds

A word may be said of the intraspinal use of the sulfonamides In the past use has been made of a 1 per cent solution of the sodium salt given in amounts 5 to 10 c c less than that of the cerebrospinal fluid removed It is probable that this measure should never be employed In the first place it is unnecessary because of the ready diffusion of the sulfonamides into the subarachnoid spaces from the blood stream secondly because it is not free from danger A few instances of

injury to the cauda equina with consequent paralysis are on record Again lumbar puncture and intraspinal treatments of any sort are not without hazard especially in the presence of an infected blood stream Instead of intraspinal use the sodium sulfonamides may be given deep in the muscle, 1 gm in 3 c c of saline solution or they may be used intravenously, the latter seeming to be preferable Finally if intraspinal therapy is really indicated, we have in penicillin an even more effective and altogether innocuous preparation for such local use

The combined use of chemotherapy and serum therapy is a matter meriting discussion While in theory an infection as serious as that with the meningococcus demands attack by every means at command, in actual practice the results of treatment by the sulfonamides alone are quite as satisfactory as those of the combined drug and serum method In the average case therefore, one is not justified in complicating matters by adding serum treatment to the accepted chemotherapy Serum may be reserved for those unusual cases giving an unsatisfactory response after adequate chemotherapy for 48 to 72 hours In such instances the treatment by serums as advised in the preceding section should be undertaken For this reason no changes have been made in the section dealing with the previously accepted methods of treatment with serum

Reverting to chemotherapy the clinician may ask what results are to be looked for in the average case Within 24 hours there should be a lessening of the severity of the symptoms The patient should become afebrile within 48 to 72 hours although the return to normal may be more prolonged Within 48 hours the cerebrospinal fluid or blood stream becomes sterile The cell count of the cerebrospinal fluid falls rapidly the percentage of mononuclear cells rising promptly reaching 90 per cent by the fifth day Within 10 to 14 days the fluid returns to normal The dangers of subarachnoid block with hydrocephalus are lessened by the rapid absorption of the meningeal exudate One might expect also a marked reduction in the metastatic complications of meningococcemia, such as arthritis peri and endo carditis, otitis media epididymitis The mortality in properly managed cases should not exceed 15 per cent In most epidemics that reported has been much lower in a few attaining zero

Penicillin — The results of the treatment of meningococcic infections with penicillin[64 69] appear to be quite as striking and brilliant as those attained from the sulfonamides It may well be that when this substance is more widely available its use will be the treatment of choice in the disease under discussion

Penicillin does not penetrate the cerebrospinal spaces from the blood stream as satisfactorily as do the sulfonamides Intraspinal administration therefore is necessary

As in other infections penicillin is given either intramuscularly or by vein If the former method is chosen 10 000 to 20 000 units are given every 3 hours day

and night until the acute symptoms are controlled If the intravenous route is preferred 100 000 units or more may be given every 24 hours in normal saline solution to which 5 per cent glucose may be added by the continuous drip method

Intraspinal treatments are given daily or on alternate days The solution of penicillin must be freshly made and should contain 10 000 to 20 000 units in each c c of normal saline The dose is 1 c c of such a solution Ordinarily not more than 3 intraspinal treatments are required

Prevention of Relapse —To forestall relapse it is important to continue treatment until the infection is under control When the patient has become afebrile treatment with a sulfonamide or with penicillin should be continued with perhaps lessened vigor for 3 or 4 days and then such medication can be discontinued

Waterhouse Friderichsen Syndrome —Management of the Waterhouse Friderichsen syndrome[7, 13] or fulminating meningococcemia with shock and adrenal *hemorrhages resolves itself into the treatment of bacteremia toxemia and shock* The bacteremia is combatted by massive doses of sulfadiazine 5 gm of the sodium salt intravenously and 8 gm orally as an initial dose followed by large doses by mouth until 25 to 30 gm have been given This dosage is controlled by the blood levels of sulfadiazine the optimum concentration being 15 to o mgm per 100 c c Instead of sulfadiazine massive doses of penicillin may be used and have been successful Two hundred fifty thousand units of penicillin may be given within a period of 24 hours The simultaneous use of antimeningococcus serum is advised in some quarters 60 000 to 120 000 units intravenously during the first 24 hours Shock is treated by heat stimulants and parenteral fluids Three thousand c c of normal saline with 5 per cent glucose may be given within a 24 hour period Five hundred c c of plasma should be given and repeated in 12 hours The theoretical advantage of adrenocortical hormone substitution therapy in this syndrome is not borne out in practice It is of questionable value though its judicious use is harmless

Treatment of Complications

Subarachnoid Block or Hydrocephalic Meningitis —Doubtless this complication may be prevented in some cases by repeated drainage of the subarachnoid system by lumbar puncture at twelve hour intervals a procedure which tends to prevent stagnation of the current of the cerebrospinal fluid and resulting adhesions This method should be carried out with thoroughness in cases with thick cerebrospinal fluid Aspiration of the fluid in such a case should be attempted with the greatest gentleness and caution If great restlessness uncontrollable headache not relieved by lumbar puncture with respiratory irregularities de

injury to the cauda equina with consequent paralysis are on record Again lumbar puncture and intraspinal treatments of any sort are not without hazard especially in the presence of an infected blood stream Instead of intraspinal use the sodium sulfonamides may be given deep in the muscle, 1 gm in 3 c c of saline solution or they may be used intravenously the latter seeming to be preferable Finally if intraspinal therapy is really indicated, we have in penicillin an even more effective and altogether innocuous preparation for such local use

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by the intravenous injections of normal saline or a 10 or 20 per cent solution of glucose

Metastatic Lesions — Metastatic meningococcic lesions may appear in joints pericardium endocardium eye lung pleura or epididymis rarely else where Treatment of meningococcic arthritis is not important since the condition is self limited and leaves no serious sequelæ If pain and swelling are great the joint exudate may be withdrawn by aspiration and serum introduced Meningococcic pericarditis with effusion has been treated successfully by aspiration of the exudate and the injection of 30 c c antimeningococcic serum into the pericardial sac Endocarditis seems to be a hopeless condition However a series of large intravenous injections of serum or sodium sulfadiazine should be tried

The panophthalmitis may be treated in its early stages by moist cool compresses care being taken not to inflict injury, by the instillation of atropin to dilate the pupil and by the intravenous injection of serum in the hope of influencing this metastatic focus of infection Netter reports success in retaining vision in two cases following the injection of serum into the vitreous The question of the enucleation of the eye destroyed by this process is important If the damaged eye is a source of prolonged pain and fever as is so often the case enucleation usually is advisable and striking improvement in the patient s general condition follows The operation should not be undertaken too early Several weeks from the time of onset ordinarily should be allowed to elapse as too early removal has resulted in renewed generalization of the infection Sympathetic ophthalmia does not occur

Any metastatic meningococcal lesion demands judicious chemotherapy in accord with that already outlined in the section on Chemotherapy

Postmeningeal Phase — The postmeningeal phase characterized by headache fatigability vasomotor disturbances intolerance of sunlight weakness of the lower extremities and exaggerated reflexes usually is cured by time It is possible that small doses of potassium iodide assist in clearing up the slowly absorbing exudate in the meninges which is the undoubted pathological basis of many of these symptoms The feeling of inadequacy and the lack of initiative and energy characterizing the period of convalescence have to be met by appropriate psychotherapy Most of the cranial or peripheral nerve palsies disappear within a few weeks those persisting for more than six months usually are permanent and inclusive of affection of the eighth nerve rarely are susceptible of improvement

lirium and great suffusion of the face suggest inflammatory swelling of the cranial contents venesection as advised by Fairley and Stewart, with or without subsequent injection of glucose in 20 per cent solution, as recommended by Haden, is indicated

If block is established, immediate action is called for before serious anatomical changes result Delay must not be allowed Puncture of the lateral ventricle through a trephine opening in adults or the lateral angle of the anterior fontanel in infants should be done promptly and is not a formidable operation As much fluid as may readily be withdrawn is removed and a slightly smaller amount of serum injected If necessary this may be repeated each twenty four or forty eight hours until drainage by the lumbar route is reestablished, or until the patient s general and local symptoms are favorable There are two alternatives to this (1) S A Cobb s method which consists of chloroform anesthesia to relax the neck muscles lumbar puncture leaving the needle in place, and the vigorous manipulation of the head and neck In some cases by this measure, which as Cecil Wall has shown folds and unfolds the pia arachnoid which forms a bridge between the cerebellum and the posterior surface of the medulla, tenuous adhesions in this neighborhood have been broken through and drainage reestablished The method is not without its dangers but is quite justifiable as an effort toward relief of this serious condition

( ) Puncture of the cisterna magna as devised by Wegeforth Ayer and Essick [4] may be of service in furnishing drainage and administering serum Cistern puncture is performed by introducing a small lumbar puncture needle in the midline of the back of the neck just above the spine of the axis in the direction of a plane passing through the glabella and the upper edge of the external auditory meatus The needle slips into the cistern with a very definite tactile impression when the resistance of the occipito atlantoid ligament and the underlying dura is overcome In an adult the cistern lies at a distance of from 3 to 5 centimeters from the skin and is 1 5 centimeters in depth The chief danger of the method is injury to regional veins and hemorrhage into the fourth ventricle but this should not be a deterrent in case a block has proved resistant to other measures

In cases of hydrocephalic meningitis surgical drainage of the subarachnoid system usually is not successful The attempt to establish drainage by inserting two lumbar puncture needles at different levels and irrigating through with saline solution is justifiable but rarely successful

To be effective treatment of block must be early and vigorous In the stage of subacute or chronic hydrocephalic meningitis, with its attendant emaciation bed sores clouded mind exaggerated reflexes and irregular temperature, little can be accomplished, as a rule but a thorough trial should be made of all judicious surgical measures a high caloric diet enforced and the body fluids maintained

by the intravenous injections of normal saline or a 10 or 20 per cent solution of glucose

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CHAPTER IV-A

THE WATERHOUSE-FRIDERICHSEN SYNDROME: FULMINATING SEPTICEMIA, USUALLY MENINGOCOCCIC WITH ADRENAL HEMORRHAGE

By HENRY A. CHRISTIAN

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Definition.—Waterhouse-Friderichsen syndrome, sometimes called purpura fulminans, is a fulminating septicemia, in most instances with marked bacteremia and extensive hemorrhage into the adrenals. A combination of overwhelming infection and acute adrenal insufficiency, as would be expected, this causes stupor, cyanosis or pallor, vomiting, low blood pressure, collapse, oliguria or anuria, usually fever and a rapidly developing purpuric type of skin lesion. Most frequently the meningococcus is the cause, but other bacteria, such as the pneumococcus, the streptococcus and the staphylococcus, can cause the same clinical condition.

History

Although named after Waterhouse and Friderichsen who made reports on it in 1911[1] and 1918,[2] respectively, as so often happens others described the condition at an earlier date. According to Weinberg and McGavack,[3] Voelcker in 1894 described a case of this condition in a pathological report from the Middlesex Hospital, London. In 1901 Little[4] recognized this clinical entity. No doubt careful search would reveal other early descriptions of it in the literature.

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Incidence

At first considered a rare disease or disease combination, recently reports of it have been appearing in increased number and so no longer can it be regarded as a very unusual clinical syndrome although still infrequent except when meningococcus infection appears in large numbers as has happened among military personnel in World War II In 1936 Aegerter[6] collected 55 cases from the literature and added 2 of his own In 1937 Sacks brought this total up to 64 In 1942 Rucks and Hobson[8] found 101 recorded cases, and early (January) in 1945 Weinberg and McGavack[3] raised the number of reported cases to 157 Since then 12 more cases have been reported

As to age incidence Lindsey and associates[9] state that more than 90 per cent of the patients were under 9 years of age and Marangoni and D Agati[13] that 70 per cent were under years of age At the other extreme is the recovered case of Weinberg and McGavack[3], a woman of 63 Recently cases reported in adults seem to have been on the increase as might be expected from the present incidence of meningitis In 485 cases of meningitis reported from army camps[10 14] the incidence of Waterhouse Friderichsen syndrome was 3 3 per cent of this total Such figures indicate that in the presence of epidemics of meningitis a not inconsequential number of cases with this syndrome should be expected and closely watched for since a very early recognition of the presence of the condition is most essential to success in treatment

Etiology

As already indicated while meningococcic septicemia is by far the most frequent cause[7 10] [4 31 33 34 35] other bacteria, such as pneumococci, hemolytic streptococci and staphylococci may be causative[3] In 12 recovered cases[3] blood cultures showed meningococcus 5 times *Staphylococcus aureus* once and pneumococcus once In 2 others of this group meningococci were obtained from the spinal fluid, and in one with sterile blood culture the patient s serum subsequently gave a positive complement fixation test for meningococci These cases indicate the marked preponderance of the meningococcus in the etiology of the Waterhouse Friderichsen syndrome

Pathology and Pathogenesis

The chief lesions seen in these patients are of two types They are (1) the lesions indicative of a very severe intoxication of short duration caused by bacterial infection and (2) lesions in the adrenal of a nature to cause severe adrenal

insufficiency In addition there often is evidence of the hepatorenal syndrome (Marangoni and D Agati[13]) and sometimes parenchymatous changes in the central nervous system consisting of congestion and edema with capillary thrombosis followed later by inflammatory perivascular infiltration of polymorphonuclear leukocytes (Banks and McCartney[16?]) In some patients, in addition to these there are varying degrees often slight, of meningitis with pleocytosis of the spinal fluid

The pathogenesis of the parenchymal lesions seems related to two factors mainly the effects of bacterial toxins and to a less extent to the circulatory insufficiency caused by injury to the adrenal glands These separately or together will explain the cell degenerations observed in the adrenals liver kidneys heart and possibly the central nervous system while the circulatory insufficiency would explain the appearance of fluid in serous cavities and in part the renal insufficiency As these patients almost always show culture evidence of septicemia usually with marked bacteremia there is ample source for bacterial toxins Since so many of these patients succumb in a very short time histological evidence of cell degeneration often is not marked although very diffusely distributed throughout the body It is true however that, when the patients live longer more cells show evidences of necrobiosis such as central necrosis of the liver and degeneration of the cells lining the renal tubules[15] all of this suggestive that the paucity of histological change in the cells of many of these cases is related more to the short duration of the action of a very toxic substance than to slight toxicity or absence of toxicity

The adrenal insufficiency is related to injury to the adrenal glands injury usually in the nature of extensive hemorrhage but sometimes apparently in the nature of non hemorrhagic, degenerative changes The cause of the adrenal hemorrhage seems to be of the nature of the effect on the blood vessels of bacterial toxins It is to be recalled that most of these patients have had rapidly developing hemorrhagic skin lesions and at autopsy commonly show subserosal hemorrhages of pleura pericardium and peritoneum

At autopsy the most striking lesion present in many patients is swelling of the adrenals with extensive sometimes massive hemorrhage into the parenchyma In 55 collected cases 51 showed bilateral and 3 unilateral hemorrhage causing disorganization of the adrenal structure However not in all reports are adrenal hemorrhages so frequent Williams[15] found them in only 0 of 17 fatal cases

Marangoni and D Agati[13] have stressed particularly degenerative changes in the liver and kidneys of patients dying with the Waterhouse Friderichsen syndrome especially in those of fairly long duration calling it hepatorenal failure or the hepatorenal syndrome and making it responsible for initial anuria with subsequent oliguria They describe in the liver in one case of 80 hours duration central

Incidence

At first considered a rare disease or disease combination, recently reports of it have been appearing in increased number, and so no longer can it be regarded as a very unusual clinical syndrome, although still infrequent except when meningococcus infection appears in large numbers as has happened among military personnel in World War II In 1936 Aegerter[6] collected 55 cases from the literature and added 2 of his own In 1937 Sacks brought this total up to 64 In 1942 Rucks and Hobson found 101 recorded cases, and early (January) in 1945 Weinberg and McGavack raised the number of reported cases to 157 Since then 12 more cases have been reported

As to age incidence Lindsey and associates[9] state that more than 90 per cent of the patients were under 9 years of age and Marangoni and D Agati[13] that 70 per cent were under 2 years of age At the other extreme is the recovered case of Weinberg and McGavack[3] a woman of 63 Recently cases reported in adults seem to have been on the increase as might be expected from the present incidence of meningitis In 485 cases of meningitis reported from army camps[10,14] the incidence of Waterhouse Friderichsen syndrome was 3 3 per cent of this total Such figures indicate that in the presence of epidemics of meningitis a not inconsequential number of cases with this syndrome should be expected and closely watched for since a very early recognition of the presence of the condition is most essential to success in treatment

Etiology

As already indicated while meningococcic septicemia is by far the most frequent cause[7,10,0,4,31,33,34,35] other bacteria, such as pneumococci, hemolytic streptococci and staphylococci may be causative[3] In 12 recovered cases[3] blood cultures showed meningococcus 5 times, *Staphylococcus aureus* once and pneumococcus once In 2 others of this group meningococci were obtained from the spinal fluid, and in one with sterile blood culture the patient s serum subsequently gave a positive complement fixation test for meningococci These cases indicate the marked preponderance of the meningococcus in the etiology of the Waterhouse Friderichsen syndrome

Pathology and Pathogenesis

The chief lesions seen in these patients are of two types They are (1) the lesions indicative of a very severe intoxication of short duration caused by bacterial infection and (2) lesions in the adrenal of a nature to cause severe adrenal

headache and generalized muscular pains of 24 hours duration he was seriously ill but rational and oriented the body was covered with numerous petechiae and purpuria areas[1] A 63 year old woman was admitted in deep stupor within one hour after she had collapsed at work the evening before this she had had a mild headache on admission the skin showed many petechiae e pecially over extremities and head and a diffuse purpuric rash chiefly over the trunk An 18 year old soldier was admitted to a station hospital complaining of headache nausea and pains in back and neck three hours later he became delirious and irrational and then petechiae were first observed [4] In children the time between any appreciable symptoms and severe illness with stupor coma or delirium may be only a very few hours

The symptoms of the developed disea e are in varying combinations head ache restlessness abdominal pain vomiting diarrhea prostration to collapse stupor coma or delirium cyanosis or pallor hemorrhagic skin lesions (petechiae or diffuse purpuric areas) sweating dyspnea piked type of fever sometimes as high as 106 to 108 F or no fever or even subnormal temperature The pul e is rapid and very weak often almost imperceptible Respiration is apt to be rapid and shallow Vein frequently are o collapsed as to make difficult intra venous injections of any sort Blood pressure as a rule is low with such readings as 63/35 80/50 60/40 80/60 70/45 100/50 60/0 in individual patients Cyanosis of lips and fingers is een often Leucocytosis may or may not be present In some patients the patient is so overwhelmed by the infection which kills within 24 hours that there is no leucocytosis or even a leucopenia However leucocytosis is usual with such top counts in individual cases as 18 900 30 200 33 000 47 250 49 350 66 950 and 73 150 Oliguria or anuria is not uncommon anuria may be among the first signs of illness There may be slight edema of the face as in acute Bright s di ease[13]

Often renal function is greatly decreased with nitrogen retention the level of non protein nitrogen substances rising as the illness continues only to fall if recovery is going to take place Creatinin tends to a proportionately higher level than would be expected from the figures obtained for total non protein and urea nitrogens The urine usually shows albumin and casts and sometimes red blood cells The pleen is not palpable the liver may be slightly enlarged

Consciou ne s often is retained when it is not Banks and McCartney believe there is a distinct parenchymal brain lesion such as described by them and already quoted in the previous section Reflexes usually are decreased A positive Kernig s sign is unusual The neck may be painful and stiff but often is not Lumbar puncture may how no slight or marked pleocytosis increased protein in it is common Sodium and chloride content of the blood plasma has been determined in a few cases sodium and chloride may be normal slightly in

vein and sinusoidal engorgement with marked dissociation of liver cords with necrotic and pigmented or vacuolized liver cells except in the peripheral part of the liver lobules and moderately intense, diffuse, polymorphonuclear and lymphocytic cell infiltration of the perilobular connective tissue, while in another of 88 hours survival these changes were much more extensive, so that not even the cells in the peripheral zones of the liver lobules showed freedom from vacuolization and granular degeneration In the last case fatty metamorphosis of liver cells was prominent and in the liver there were numerous areas of hemorrhage and polymorphonuclear leucocytic infiltration In contrast, in patients living for only 24 hours liver changes were slight and limited to central zones of the liver lobules while in one of 40 hours duration liver changes were more marked than in the preceding but not so extensive and marked as in those just described in cases ill for 80 and 88 hours

In the kidneys of these cases there were such changes as albuminous degeneration of the cells of the convoluted tubules with albuminous deposits in their lumina and avascularity and increased cellularity of the glomeruli, more marked in those living longer and less evident in those of shorter life

The heart usually is dilated especially the right auricle and to a somewhat less degree the right ventricle Cardiac hypertrophy is not infrequent The heart muscle shows cloudy swelling sometimes fragmentation of the muscle cells not infrequently some interstitial edema Slight pericardial effusion is not uncommon Considerable hydrothorax up to 500 c c and ascites up to 1,000 c c may be found

In some patients there are parenchymal central nervous system changes, encephalitis as described by Banks and McCartney[17] whose description is quoted in the first paragraph of this section as well as varying degrees usually slight, of meningitis Not infrequently the polymorphonuclear cells of the circulating blood contain numerous meningococci What happens to the adrenals in recovered cases is not known at present Where hemorrhage into the adrenals has been extensive as often it is, presumably in healing injury to the adrenals must be a residual possibly later to become a cause of chronic adrenal insufficiency or Addison s disease

The fulminating character and very brief duration in some patients may make the cause of death in them of medicolegal interest[44]

Symptoms

Onset is abrupt so that in a few hours the full blown clinical picture is present Such histories of the early hours of the disease as the following are not unusual A 20 year old male was admitted to the hospital complaining of chills fever,

patient Weinberg and McGavack[3] reported on Jan 25 1945 and of Hayes and Whalen[7] reported on March 17 1945 These recent reports suggest for the future a much better immediate prognosis for these cases What the long time prognosis is to be in relation to permanent damage to the adrenals remains to be seen No recovered cases have been reported so far as to this It seems likely that some recovered cases will progress into Addison s disease with its usual symptoms and signs

TREATMENT

In treatment the dual causes of the Waterhouse Friderichsen syndrome must be kept in mind These are (1) the effect of overwhelming bacterial infection and (2) adrenal insufficiency As both effects develop with very marked celerity each must be met at the earliest possible moment and the treatment of each be pushed to its maximum of effectiveness abetted by measures appropriate to counteracting shock

Treatment of the Infection —This calls for the use of chemotherapy begun at the earliest possible moment and continued at high level of blood content until the infection and its toxicity are overcome Cured cases reported to date have received sulfonamide sulfadiazine in all except 3 earlier cases with or without the addition of serum specific for the infecting organism or penicillin (1 case)

It seems advisable to give the first dose of sulfadiazine intravenously in the form of the sodium salt in a dose of 5 gm repeated until a blood level of about 15 mgm per 100 c c is reached If the patient is in condition to take the drug by mouth mouth dosage can be added or substituted giving 4 gm in the first dose and then 2 gm every 4 hours governing the exact amount of drug to be given by the two routes from the blood level reached It is to be remembered that these patients usually have defective renal function with varying azotemia This means slowed excretion of the sulfonamide and so the possibility of toxic retention making it still more important to guide dosage by blood level and guard against precipitation of sulfonamides in the kidney by giving an increased fluid intake intravenously or by mouth and possibly alkalinization of the urine by doses of sodium bicarbonate

On account of the features just mentioned penicillin would seem preferable to sulfadiazine given intravenously by continued drip totaling 300 000 to 400 000 units per 24 hours or intramuscularly 20 000 to 40 000 units every 3 to 4 hours with in addition an initial intrathecal dose of 15 000 to 20 000 units repeated if there is evidence in spinal fluid of meningeal infection or meningitis So far there is record of one case treated with penicillin When the latter are available in some number a decision can be made between sulfonamide or penicillin treatment as to which is most effective

creased or slightly decreased beyond the levels considered to be normal, since two processes are acting adrenal insufficiency tending to decrease them and renal insufficiency tending to increase them When determined, potassium has been found within normal limits in the blood

The skin lesion is petechial progressing quickly in most patients to small or large areas of purpura as shown in the illustration Fig 3 in the preceding chapter often the skin lesions are dark blue or violaceous in color

The clinical picture in these patients is one of shock In some respects this is the shock of overwhelming sepsis in other respects it is the shock of acute, critical, adrenal insufficiency There is full evidence from the clinical study of these patients and in the lesions found at autopsy supporting the belief that both of these processes are operative in combination

Diagnosis

The symptoms just described should suggest the diagnosis Certainty of diagnosis in an etiological sense is brought by finding bacteria usually meningococci in the leucocytes in blood smears made from the circulating blood[11,] or from blood squeezed from the skin lesions[19, 1] or in smears made from spinal fluid Positive cultures from blood or spinal fluid are of the same positiveness in diagnosis but cultures take too long for diagnosis in a condition so fulminantly acute as this in which recovery depends in very large measure on instituting correct treatment at the earliest possible moment Certainty of diagnosis of the adrenal lesion is only in autopsied cases It can be inferred from the clinical picture In recovered cases obviously it only can be inferred If with rapidly developing symptoms of a severe infection a petechial rash appears a presumptive diagnosis of Waterhouse Friderichsen syndrome should be made and treatment for it instituted immediately Fortunately the two most essential parts of the treatment are the same whether the condition is caused by the meningococcus pneumococcus streptococcus or staphylococcus

Prognosis

When this chapter was first published i e on September 1, 1938 I wrote in it "so far all cases have been fatal often in less than 24 hours Untreated the prognosis remains completely bad probably all untreated cases die although survival up to 80 and 88 hours[13] has been reported With prompt treatment as outlined in the next section survival can be accomplished In 1940 Carey[6] reported the first recovery Since then 15 other recoveries have been reported[3, 8, 11, 1, 1, 3, 7, 9, 33, 35, 36, 37] the recoveries most recently reported being the

patient Weinberg and McGavack[5] reported on Jan 25 1945 and of Hayes and Whalen[33] reported on March 17 1945 These recent reports suggest for the future a much better immediate prognosis for these cases What the long time prognosis is to be in relation to permanent damage to the adrenals remains to be seen No recovered cases have been reported so far as to this It seems likely that some recovered cases will progress into Addison s disease with its usual symptoms and signs

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Whether it is best to use the appropriate type specific antiserum or anti toxin or not has not been determined Some patients have received serum in addition to a sulfonamide and 60 000 to 120,000 units have been advised for the first 24 hours given intravenously

Treatment of Adrenal Insufficiency — The use of an active adrenal cortical extract seems advisable although some express doubt of a real need for it However reports of some cases indicate an effectiveness much as is obtained by its use in the acute crises of Addison s disease Adrenal cortical extract, 20 c c in 500 c c of 2 per cent sodium chloride solution containing 5 per cent glucose given slowly by intravenous route has been advised, with repetition based on the blood pressure In addition to this there should be used 15 mgm of desoxy corticosterone given intramuscularly and repeated in 10 mgm doses every 8 hours until systolic blood pressure has been maintained above a level of 100 mm Hg This therapy with adrenal substances seems a rational procedure and is advised for the present When more cases have been treated and reported, then it will be possible to assess better the need for the use of adrenal cortical extract and desoxycorticosterone in addition to a sulfonamide or penicillin

Treatment of Shock — As in all other forms of shock the best therapy for it is its prevention by prompt control of the infection If sulfadiazine or penicillin can be given before shock develops that is the ideal to be sought The prompt use of adrenal substance may be an important addition to prophylaxis against shock When evidences of shock appear transfusions of plasma or blood as used in other forms of shock are to be given Fluid intake also must be at a level to counteract any dehydration that may be in evidence Much of the treatment involves intravenous fluid intake and the amount of this must be taken into account With the circulatory collapse of such a severe infection and of adrenal insufficiency it is to be remembered that in these patients part of the circulatory insufficiency may be and probably is derived from myocardial insufficiency caused by damage from bacterial toxin and so caution is needed in giving fluids to make certain that in the effort to counteract dehydration the heart does not receive an overload of blood bulk and the effective action of the circulation be hindered Careful watch should be kept for evidences of pulmonary edema pleural fluid and liver congestion as signs of cardiac insufficiency If found, these indicate that the patient has received too much fluid or fluid too rapidly

Drug treatment of circulatory insufficiency in these cases probably does little or no good and may do harm Digitalis is not indicated and should not be used unless the patient has had some form of chronic cardiac disease prior to develop ing the Waterhouse Friderichsen syndrome Coramine epinephrine or caffeine may help and can be used cautiously repeated dosage is advisable if improve ment follows the use of one of these

Treatment of Continued Adrenal Insufficiency — The possibility of this during convalescence and later should be kept in mind and signs and symptoms looked for If these are found continuation of treatment appropriate to adrenal insufficiency as described under Treatment in the discussion of Addison s disease elsewhere in Oxford Medicine should be carried on

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CHAPTER V

POLIOMYELITIS

By JAMES L. WILSON

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INTRODUCTION

Acute anterior poliomyelitis is an acute contagious disease of the central nervous system caused by a filterable virus. The name describes the very specific anatomical localization of the most characteristic pathological changes due to this disease. It refers to the unique tendency of the virus to attack the anterior part of the gray matter of the spinal cord. The disease is known most commonly in English speaking countries as infantile paralysis, a name which is well established by custom but misleading as it implies a predilection of the disease for infants. It is also known, particularly in European countries, as Heine-Medin disease after Heine[1], a German who in 1860 gave one of the first accurate descriptions, and Medin, a Swede, who also described it with excellent epidemiological observations as early as 1890. This disease probably has been prevalent for a great many years and in descriptions or old pictures of its disastrous results there are hints of its occurrence that antedate the Christian era. It is, however, only in the last seventy five years that any definite description of it as a clinical entity has appeared and only since Medin's description followed in a few years by the reports of Caverly[3] and Wickman[4] has any clear understanding of it as an acute contagious disease been evident.

Poliomyelitis occupies a position of tremendous importance and interest, not because of its frequency, actually far less than most acute contagious diseases, but because of its great tendency to cause paralysis and to leave in its wake permanent cripples. In spite of Medin's report

fifty years ago up to relatively recent times knowledge of this disease generally has been limited to study of paralyzed patients and no recognition of victims of the disease who did not become paralyzed was evident in medical literature. Mortality figures for different years are not comparable since in the past the diagnosis of infantile paralysis depended upon the recognition of a state of paralysis while in recent years more accurate diagnosis has led to the recognition of a variable but increasing number of non-paralytic patients.

Probably no disease at present is being more intensely studied by more men.[8] Investigations are going on in most of the major medical centers of this country and large sums of money are ready to aid anyone with an intelligent program of study. So far no effective plan for the control or prevention of the disease or for treatment once it has occurred has been developed. Work now going on is proving, however, immensely profitable. New knowledge about filterable viruses is being rapidly acquired.

This article will concern itself primarily with a description of the clinical course of the acute stage of the disease and no attempt will be made to discuss thoroughly either the interesting immunological and epidemiological knowledge that is being acquired so rapidly nor the orthopedic aftercare which, by attempts to salvage what is left after the disastrous disease has subsided, makes up most of what medicine has to offer in the way of treatment.

Summary of Clinical Course

The mode of dissemination and portal of entrance of the virus of poliomyelitis is by no means well understood. It is probably widespread in any epidemic and enters the body either by the intestinal tract or the mucous membranes of the nose and throat. After an incubation time of one to two weeks a febrile illness occurs with fairly characteristic meningeal signs. At this time the spinal fluid shows a moderate increase in cell count. During the febrile stage of the disease, which usually lasts four or five days,[9] considerable muscle pain may be present and paralysis, if it is to occur, will appear. The paralysis is apt to be spotty and asymmetrical. Probably a quarter of the patients at least escape without any paralysis and it may be only slight in a considerable proportion of the others. Death occurs in a small percentage due to paralysis of the muscles of respiration or to paralysis of the throat associated with destruction of

some of the "vital" centers of the medulla In the patients surviving with paralysis a variable degree of improvement takes place over a period of weeks and months but much of the paralysis is permanent

Types and Stages of the Disease

It is well at the beginning to define several terms which are used commonly in discussing infantile paralysis

The *preparalytic stage* of the disease is obviously the course up to the point of recognition of paralysis Since paralysis may not, after all occur this term may not apply and we may speak then of a *non paralytic* course of the disease

Abortive poliomyelitis is a term used commonly but not consistently defined by different writers By some it refers to a mild nondescript illness which may occur without any central nervous system symptoms and which is presumed to be due to the virus of poliomyelitis only because it occurs in members of a family coincidentally with an acute and definite case of poliomyelitis Others use the term abortive poliomyelitis for the non paralytic form of the disease diagnosed because of the clinical symptoms and characteristic changes in the spinal fluid We will use the term when we do use it in the first sense that is as an illness presumed to be due to the virus of poliomyelitis not involving the central nervous system seen in a family with other cases suffering from definite poliomyelitis

An *encephalitic form* of the disease is described and the term obviously indicates a type where sensorium changes are more marked than usual The use of the term in this sense should not imply that the usual signs of encephalitis are seen in poliomyelitis such as convulsions changes in personality or neurological sequelae such as upper motor neuron defects The encephalitic form of the disease so called is associated frequently with bulbar poliomyelitis

Bulbar poliomyelitis is a term commonly used but it is not an exact one Strictly speaking it distinguishes one form of the disease from the more usual spinal form by the anatomical location of the major pathological lesion and the term should be used only where the disease attacks the medulla or bulb of the brain and manifests itself by disturbances of the respiratory and vasomotor centers and by paralysis of muscles known to be innervated from the medulla those of the soft palate pharynx and larynx However the term often is used carelessly for paralyses of muscles innervated from above the medulla as from the pons such as

ocular motor paralysis. The term is carelessly and wrongly used to refer to any type of respiratory difficulty such as paralysis of the intercostal and diaphragmatic muscles, obviously high spinal and not bulbar in origin. The term will be used in this chapter in the usual though inexact sense referring to brain stem involvement. It is too bad that the term is implanted in medical terminology, since it would be clearer and more practical to refer only to the paralyzed muscle groups as palatal, pharyngeal, facial or ocular motor paralysis.

Clinical Picture

General Aspects

As epidemics occur and are observed and described carefully, it is noted that from season to season there is a change of emphasis by different observers on certain minor features. This is undoubtedly due to an actual change in the superficial characteristics of the disease. Although great variability of symptomatology from patient to patient occurs in any epidemic, it is apparent that in some years there is a great deal more muscle pain and tenderness described than in others, that in some epidemics abdominal pain is a common symptom, while in others diarrhea is frequent. Physicians in any epidemic quickly learn to detect very minor characteristics which to them at that time become of great importance and enable them to become very skilled and adept in making an early diagnosis. These characteristics may be described, but there is danger of overemphasizing them at the expense of more consistent and dependable diagnostic features.

Outline of Course

The course of poliomyelitis is as definite and points as dependably to a diagnosis as does the clinical picture of any disease entity. This statement should not imply that there are not frequent wide variations. The clinical picture is best studied in the light of the usual sequence of events which divides itself quite naturally into definite periods, and the differential diagnosis is best discussed with different emphasis for each period at which the disease may first be encountered. Figure 1 shows graphically the course. It is always worth while to plot carefully in one's mind the

times of onset and sequence of symptoms Acute poliomyelitis is a disease of short duration and its course and the time intervals do not vary much from that shown in Fig 1

The ordinary febrile course consists of a rise of temperature associated with meningeal signs with or without paralysis lasting a total of five to seven days However a certain proportion of the patients show a preliminary rise of temperature for two or three days associated with no specific symptoms which may be called a prodromal febrile stage

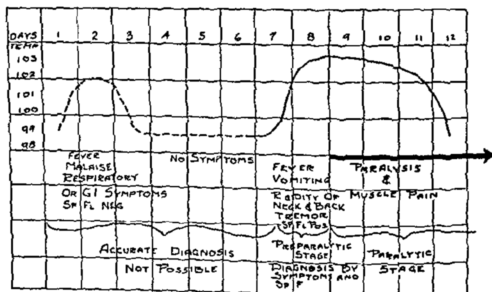


Figure 1

followed by a period of well being before onset of the ordinary febrile course It is quite possible for poliomyelitis to occur without any recognized febrile course though any such instance should be studied with reasonable skepticism

The first hump of the temperature just referred to is a prodromal febrile stage and as shown in Figure I is made much of but is seldom of aid in diagnosis It is probably emphasized too greatly for the good of students as it occurs in as little as 25 per cent of the patients, the frequency probably depending on the acuteness of the observation of the family or the physician Some good observers deny that such prodromal fevers are even a part of the disease poliomyelitis or more than a coincidental mild illness When the initial rise of temperature does occur the resulting two humped temperature curve is termed the 'dromedary

course' this expression having been used by someone who thought the two temperature peaks resembled the humps of a camel. It is unfortunate and also unimportant that the true dromedary has only one hump. The term still persists however.

Prodromal Febrile Stage

The first stage or first "hump" of the fever occurs in [illegible]0 to 30 per cent of the patients. The symptoms are non specific and diagnosis at this time is impossible. Suspicion of the disease can be aroused at that time only because other members of the family or close associates are ill with infantile paralysis. There is slight fever and malaise, sometimes a headache or various gastrointestinal disturbances which ordinarily are passed off as a slight cold or "flu" or something equally trivial. Undoubtedly the symptoms often are missed completely or not reported to the other members of the family. The spinal fluid at this stage is normal. This has been proved to be so in a considerable number of instances where because of the presence of poliomyelitis in other members of the family a lumbar puncture was done on a mildly ill child in spite of the lack of any meningeal signs and later repeated, and the spinal fluid was found abnormal in the second or meningeal stage. This so-called dromedary stage of the disease lasts, as can be seen, one to two days. There is then a period of well being of two or three days more. On the fourth to the seventh day following the first febrile rise a second rise of temperature takes place which is abrupt.

Meningeal Preparalytic Stage

Symptoms.—Three symptoms almost invariably occur at this time: fever, vomiting and headache. These symptoms obviously are common to a great many other diseases and in themselves they do not lead to any particular diagnosis. In fact the history of the symptoms at this stage can be considered only suggestive of, or compatible with, the diagnosis of poliomyelitis. The *fever* is not high, usually under 10[illegible] F. In the bulbar type of disease the fever is apt to be higher and to extend over a longer period. The *vomiting* is not like that caused by increased intracranial pressure and usually is not particularly forceful or projectile. It is associated with nausea. The *headache* is of moderate severity. Small

children may not complain of headache although its presence usually can be detected.

A great variety of pains may occur predominantly located in the back or neck. The neck pain often may not be reported as a "stiff" neck or back although occasionally one gets a very illuminating story of difficulty in walking or of a very curious stiff gait possibly attributed to a back sprain but obviously due to the 'meningeal' symptoms of the disease. Usually the patient is sick enough to stay in bed but it is not uncommon for him to remain ambulant up to the time of consulting a physician. Either diarrhea or constipation may occur. The diarrhea is not common except in occasional epidemics. Sometimes constipation is very marked and seems definitely to be associated with atonia of the gut. Abdominal pain only occasionally appears. This is in the midepigastric area and is not severe.

Physical Findings. — The *general appearance of the patient* is of some diagnostic importance but actually cannot play a great part in establishing a diagnosis. It has been often emphasized that the patient is apt to be healthy. Other general characteristics will be found discussed under the heading of 'constitutional tendencies.' It is said by many that either the patient looks sicker than he actually is or that he is sicker than he looks. These impressions probably arise from the fact that the patient is flushed and looks as if he had a temperature of 104° or 105° F. when actually his temperature is 101° or 102° F., and also from the fact that although the patient appears as if he has a high fever, he is not greatly prostrated, is apt to be alert, cooperative, even somewhat stimulated and talkative. It has been noted that the patient's skin is pink and flushed. A tache cerebral usually is demonstrated easily. This, of course, occurs in many other diseases. In many a positive tourniquet test or the easy appearance of petechiæ on squeezing some part of the skin can be demonstrated. The pulse is fast, out of proportion to the actual fever and more in proportion to the appearance of the child. Perspiration is marked and becomes more so as the disease progresses. It is such a prominent feature in some that patients drench their bedclothes and need frequent changing.

A great deal of emphasis must be put upon the detection of signs of central nervous system involvement. This emphasis is justified because it is on the demonstration of a characteristic type of stiff neck or back that a lumbar puncture is justifiably done, and a dependable diagnosis of poliomyelitis in a preparalytic stage cannot be made without a demonstration of an abnormal type of fluid. The spinal fluid shows abnormal

ines within a relatively few hours after the rise of temperature and appearance of the meningeal signs

The *rigidity of the neck and back* usually is not as marked as in meningitis and nowhere near as severe as in tetanus However this varies and can be occasionally so striking that as pointed out before even parents notice it in their children and may report a curious "stiff" type of gait The spinal rigidity is in the cervical and dorsal regions and is less marked in the lumbar areas It is safest to demonstrate it particularly in children by asking to them to carry out certain procedures Characteristically when a patient is asked to sit up he may say he can not which actually will mean that he does not want to If he can be induced to sit up unaided however a certain maneuver is characteristically carried out The patient may well be cooperative and respond quickly and show only a mild annoyance at being disturbed He will turn on his side push himself up on his hands and then turn around sitting squarely on the bed but leaning both hands behind as a prop This "tripod" position enables him to keep his balance without flexion of the spine in the ordinary way If asked to bend his head forward he will rock his head slightly on the atlas keeping his neck stiff and the chin in If asked to put the chin on the sternum or on the examiner's finger put against the sternal notch usually he will try to do so with careful jerky forward movements of his head and will open his mouth widely in an attempt to put his chin on the sternum with the minimum flexing of the neck If a patient is lifted by his shoulders even with his cooperation the head falls back as if the neck were paralyzed In fact paralysis of the neck often has been wrongly diagnosed from this characteristic action The patient allows the head to fall back not because it is paralyzed but because in that way painful flexion by his own muscle efforts is avoided If the patient has any extensive neck muscle paralysis he will not be able to turn his head from side to side which he fairly readily does without pain when no paralysis exists

A *fine tremor* often precedes by a few hours the development of paralysis This should not be too greatly depended upon however, because some patients will show quite marked tremors without subsequent paralysis developing When it is seen localized in one extremity however it can properly give the physician cause for concern

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of the extent of paralysis becomes difficult. Although tenderness and paralysis often are associated, it does not follow at all that a particularly tender muscle group will become paralyzed. A physician often has the happy experience of finding that a tender muscle group which he thought was paralyzed shows good activity when the pain ceases. On the other hand, muscle tenderness often conceals the paralysis. Particularly in children it is hard to tell the difference between inability and disinclination to move a muscle. Attempts to make an exact evaluation of paralysis is often futile in the acute stage of the disease.

Characteristics of the Paralysis. — The paralysis of poliomyelitis is one of muscle groups. It is not characteristic to have one extremity alone wholly paralyzed. The paralysis in any muscle group can be of any degree, as it is obvious that a variable number of nerve cells can be destroyed. It is therefore characteristic of poliomyelitis to cause a spotty paralysis, although all the major muscle groups of an extremity may be included at times. The disease does not bring about an interruption of function of the entire cord and so does not produce the result seen in a transverse myelitis. It does not cause a diffuse generalized weakness. Since the essential lesion is in the anterior horn cells, it follows that the pattern of the paralysis does not follow the distribution of a nerve trunk such as the femoral or the glossopharyngeal nerve. Since a nerve trunk may derive its fibers from a fairly wide source in the cord or medulla, it is wiser to think of paralysis in terms of the muscles involved rather than of the nerve trunks supplying them.

The commonest groups of muscles paralyzed are those of the arms and legs, since the disease attacks predominantly the two bulbar swellings of the cord in the cervical and lumbar regions. The occurrence of the different paralyses varies considerably in different epidemics and at different stages in an epidemic. The tables on the following page show a distribution of paralyses as characteristic now as when the studies were made.

Detection of Paralysis. — The difficulty in measuring the paralysis during the acute stage has been noted already. The lack of cooperation of young children and the pain occurring at all ages makes exact observations nearly impossible. Complete muscle examination during the acute stage, however, is harmful and should not be attempted. After the febrile period is over and most of the muscle tenderness has disappeared, a thorough examination is necessary for prognosis as well as for planning treatment. A good quantitative evaluation of the function of all muscle groups must remain the task of specially trained technicians. Over 100

Paralytic Stage

It has been stated already that paralysis may not occur. The temperature may become normal without any further symptoms and muscle pain of considerable severity may occur even if no paralysis is seen. It is associated so often with paralysis, however, that it will be discussed in this section.

Muscle pain varies a great deal in individual patients and in different epidemics. It is most marked during the early stage of paralysis and can be so severe and so localized as to imitate osteomyelitis or arthritis. On the other hand, frequently it is quite absent. The presence of pain usually is evident from specific complaint by the patient; in young children or babies the fact that pain is present should be obvious from general observation or from watching the patient while he is being handled. Too frequently nurses accustomed to "spoiled" children or to the querulousness associated with any illness do not appreciate sufficiently the amount of real distress present. Pain is greatest on stretching of the muscles involved by motion of a joint but may be detected by palpation or firm squeezing of the muscle mass. The nature of pain is different in the early febrile stage from that seen later.

Permanent damage to the central nervous system manifests itself almost wholly by *paralysis*. The disease does not affect permanently the sensory nerve cells, although it is possible that the pain of the acute stage of the disease is due to involvement of the posterior part of the cord. There is no disturbance of the senses of touch or pain. Paralysis, when it occurs, will occur usually on the second, third and fourth day after the first meningeal symptom. Occasionally paralysis will occur very rapidly in a few hours after the first sign of fever and occasionally as late as the sixth day. The peak of the incidence of paralysis is on the third day. A reasonably good prognosis against the appearance of paralysis or an extension of it can be made by the time the temperature reaches normal, which usually is by the fifth or sixth day. It may be stated again that paralysis apparently due to poliomyelitis may occur without any recognized febrile illness.

Because of pain or lack of cooperation of young patients recognition of paralysis often is very difficult and some reports of its extension late in the disease probably are due to earlier inaccurate observation. Even a considerable degree of paralysis can be missed completely, particularly of the paravertebral group of muscles and in young and uncooperative children. It is easy to understand that when pain is marked an evaluation

fully as possible at intervals of two or three months and then once again after six months or a year

Bulbar Type of Paralysis — Although in the majority of instances paralysis occurs in the trunk or in the arms and legs the disease attacks just as characteristically the lower motor neuron cells in the medulla or bulb The reported incidence of the bulbar form of the disease varies greatly and apparently it is different in different epidemics and is greater at the beginning than the end of an epidemic One bulbar paralysis to eight or ten of the spinal type would be a reasonable expectation Bulbar paralyses may well be associated with paralysis of the spinal type

A good deal of emphasis must be put upon the bulbar paralyses because of the high mortality in this group Paralysis of the face the soft palate or the pharynx are all called bulbar palsies are frequently associated and are easy to recognize Paralysis of the larynx is much more rare and is often difficult to detect clearly Aphonia is uncommon but does occur A facial paralysis usually is associated with a palatal paralysis and the latter with pharyngeal paralysis but both palatal and pharyngeal paralysis can occur alone Paralysis of the extrinsic muscles of the eyes is seen occasionally and is associated usually with one of the bulbar palsies

The recognition of a facial paralysis which is of course of the central type is easy Detection of palatal paralysis is made easy by the presence of a nasal voice and by the regurgitation of fluid through the nose on swallowing Pharyngeal paralysis likewise should be easy to diagnose but nevertheless is missed frequently through inexperience Inability to swallow due to pharyngeal paralysis should be suspected and looked for whenever there is a facial or a palatal paralysis The first symptoms may be noisy gurgling breathing and respiration which is irregular and interrupted The patient himself may not realize at first what the difficulty is and the paralysis may be demonstrated first by a severe choking attack following an attempt to drink Frequently a doctor or a nurse may demonstrate the paralysis too dramatically by offering a child a drink of water The child being thirsty will accept the water greedily and will attempt to swallow a large mouthful He then appears frightened begins to choke thrashes around the bed and finally in a paroxysm of fear aspiration and laryngeal spasm may bring about severe anoxia with coma A definite turn for the worse may occur at this moment Great care should be exercised to avoid such episodes and at the most only half a teaspoonful of water should be given when an attempt is made to demonstrate pharyngeal paralysis

Bulbar forms of poliomyelitis are associated with a longer and higher

DISTRIBUTION OF PARALYSIS IN 1916 IN NEW YORK STATE[10]

	NUMBER OF CASES
Both legs	338
One leg	30[illegible]
Both legs and both arms	127
Both legs and one arm	101
One arm	83
One arm and one leg, same side	38
One arm and one leg, opposite side	9
Both arms	33
Both arms and one leg	20
Cerebral cases	57
Facial alone	38
Total	1 166

SUMMARY OF DISTRIBUTION OF PARALYSIS THROUGHOUT THE BODY[11]

LOCALIZATION	TOTAL NUMBER OF CASES 5748	
	NUMBER	PER CENT OF TOTAL
Cranial nerve	767	13 3
Throat and neck	333	5 8
Trunk	1 601	27 8
Arm	2 37[illegible]	41 3
Leg	4 519	78 6

separate muscle groups need to be tested and their power roughly quantitated The ordinary medical attendant however, should be able to detect gross paralysis and should be particularly on the alert for certain dangerous or deforming weaknesses such as bulbar paralysis and those of the trunk Watching an infant move its extremities and body under various cutaneous stimuli can give one a rough idea of the paralysis Patient observation of all spontaneous motions requires time but is of great value For children a game can be invented easily whereby the examiner holds the child's arm or leg and then induces the small patient to resist motion in any direction The physician always should be on the alert for the late discovery of paralysis originally missed Paralysis of the muscles of the trunk particularly the abdominal muscles and the paravertebral groups is apt to be overlooked and to lead to deforming scoliosis Repeated muscle examinations should be carried out as care

Failure of Respiration — The final mechanism of death in any disease becomes almost a matter of philosophy In poliomyelitis it seems more than usually logical to say that death is brought about by an immediate interference with the mechanism of respiration Efficient respiration may be prevented by three means

(1) By disturbance of the nerve centers in the medulla or bulb which control respiration
( ) By the collection of mucus or vomitus around the glottis in patients with paralysis of the pharynx causing either by actual obstruction or by setting up irritative spasms of the glottis constantly interrupted inspiration and consequently shallow irregular and ineffective respiratory efforts
(3) By actual paralysis of the primary respiratory muscles the intercostals and diaphragm

The lesions existing in the first and second situations involvement of the respiratory centers or paralysis of the pharynx are in the medulla and therefore this type of the disease commonly and properly is called bulbar

In the third situation that with actual paralysis of the intercostal muscles or of the diaphragm the lesion exists in the dorsal and cervical cord This type of the disease therefore should not be classed as bulbar although respiratory failure occurs

The respiratory difficulty in any patient ill with poliomyelitis may be due to a single one or to any combination of these three factors Paralysis of the respiratory muscles very frequently occurs alone without bulbar complications Paralysis of the pharynx the palate or the facial muscles all innervated from the medulla very frequently is associated with apparent involvement of the vital centers most evidently the respiratory center The marvelously complicated and congested mass of nerve paths and nerve centers of the medulla makes it remarkable that such association does not occur always

In the individual patient with bulbar poliomyelitis without paralysis of the intercostal muscles or of the diaphragm often it is difficult to untangle the causes of the respiratory difficulty In some cases the respiratory disturbance seems purely central in origin and may make itself manifest by shallow irregular respirations or by jerky spasmodic inspiratory efforts sometimes almost amounting to a succession of hiccoughs

Pharyngeal Paralysis — Pharyngeal paralysis alone can interfere with respiration due to the existence of unswallowed pharyngeal secretions

temperature course and with a more rapid pulse than in the usual spinal type of disease When the disease is fatal death will be preceded by a period when the pulse is extraordinarily rapid, increasing hour by hour Rarely there is a slow vagal pulse associated with bulbar poliomyelitis The blood pressure seldom is elevated Respiratory disturbances are frequent and will be discussed in the section on failure of respiration

Landry's Paralysis — Landry described a disease with paralysis progressing in the course of a few days from the feet and legs to the trunk and upward to a fatal result with failure of the respiratory muscles or with bulbar symptoms He described also a descending paralysis with the same evidence of slow progression Certainly a picture like this occurs in epidemics of poliomyelitis and closely resembles the ordinary disease with pathological findings similar to those of poliomyelitis Whether there are other disease entities which can produce a similar picture has not been surely established but where the course is that of an acute disease with the progression of paralysis a matter of a few days, so called Landry's paralysis should be considered a particularly vicious type of acute anterior poliomyelitis

Encephalitic Type of Poliomyelitis — Although there is certainly evidence from the pathology of the disease that poliomyelitis may attack all parts of the central nervous system we can say that clinical evidence of involvement of the higher brain centers is in most instances meager However occasionally one encounters symptoms of such a nature that the expression "encephalitic type of poliomyelitis" is justified Ordinarily the victim of poliomyelitis except when in extremis, is mentally alert and shows none of the picture of encephalitis Sometimes however the sensorium is dull there is excessive drowsiness the patient is hard to arouse and presents a picture resembling that of tuberculous meningitis Except for this involvement of the general sensorium, we see little evidence of encephalitis Intellectual defects do not occur as sequelae of poliomyelitis Upper motor neuron involvement producing spastic paralysis must be extraordinarily unusual although frequently mentioned in early reports and one should view with skepticism any such condition attributed to poliomyelitis Convulsions in poliomyelitis also are so extraordinarily rare that such a symptom should be considered weighty evidence against that diagnosis Many cases of encephalitis possibly caused by a related virus have been called poliomyelitis during epidemic times At present our knowledge of virus strains does not justify the inclusion of such widely different clinical pictures even though the seasonal incidence is similar

are evident during the acute stage of the disease even though they are hard to define, vary in intensity and might be considered no more prominent than in some diseases which do not attack the central nervous system. Even without definite paralysis the patient is as weak and unsteady as after any febrile illness. Complaints of easy fatigue, of tachycardia, of constipation, of easy flushing and of perspiration are made often and should be treated by rest and protection from overwork over a long period of convalescence.

In view of the morphological evidence of widespread involvement of the central nervous system demonstrable after death during the acute stage of poliomyelitis, it is worthwhile emphasizing that certain symptoms which might be expected to occur are not seen. Except in so-called bulbar poliomyelitis there are no immediate disturbances in blood pressure. Although there are some ill defined sensations in the skin which one might call paresthesia, there are no definite changes in sensation such as loss of temperature sense or anesthesia. Although in certain forms of the disease the sensorium may be dull and confused, sometimes due to anoxia, there are no permanent changes in the sensorium and intellectual impairment need not be feared. Except extraordinarily rarely and then in questionable circumstances, convulsions do not form part of the symptomatology of poliomyelitis. In spite of the fact that many other parts of the cord than the motor cells are involved in the acute disease, only lower motor paralyses need be expected as permanent sequelae and the findings of any other neurological defect should cause the physician to review his diagnosis with great skepticism.

The detection of paralysis has been discussed already. Paralysis of the bladder, of the gut, of the palate, of the pharynx and of the larynx fairly promptly disappear and there will be a considerable but a greatly variable improvement in other paralyses. The early absence of demonstrable paralysis should not be accepted as final. Muscle examination should be repeated at intervals in all patients, especially in small children. In extensively paralyzed patients hypertension occasionally occurs after many weeks. The mechanism of this as yet is not clearly understood. Renal calculi are seen not infrequently in patients kept in a recumbent posture or in casts.

or vomitus which prevents the passage of air freely through the larynx. In pharyngeal paralysis often it is very difficult to be sure that there is not also some disturbance in the medulla of the nerve centers themselves controlling respiration. It seems reasonable to hope that there is no central disturbance of respiration when the patient appears to be consciously trying to breathe carefully to clear his throat and seems to be alert to his own difficulties. The patient for many hours may need to breathe with every respiration in a carefully calculated effort to avoid aspiration. Due to cumulative fatigue and anoxia alert consciousness soon may be lost and be followed by a stage of semi coma with occasional periods of consciousness and fright so that the condition is hard to distinguish from a condition due to a primary encephalopathy. A very rapid pulse is characteristic of the bulbar form of poliomyelitis before death and is evidently a manifestation of the disturbance of the vagus nerve as well as the result of simple excitement and fatigue.

Respiratory Muscle Paralysis. — The early evidence of paralysis of the intercostal muscles or of the diaphragm may be difficult to recognize and to interpret. Wakefulness, anxiety, restlessness, an increase in respiratory rate, the use of the alae nasi, a slight respiratory grunt, disinclination to talk or a curious frequently interrupted monosyllabic speech all may precede more marked evidences of paralysis. None of these signs are of course specifically indicative of paralysis of the muscles of respiration but should demand very careful examination. Cyanosis indicates severe paralysis and does not precede death by many hours.

In a child who will not cooperate by "taking a deep breath" it may be helpful in the demonstration of a partial paralysis of the muscles of respiration to inhibit the action first of the intercostals and then of the diaphragm by splinting the chest or the abdomen with the hands and thus forcing the alternate respiratory muscles to greater action. Paralysis of both shoulders is associated so frequently with paralysis of the intercostal muscles that when this is detected in the acute stage of the disease where further extension might occur the respiratory muscles should be watched carefully and the possibility of the need for artificial respiration in the near future kept in mind.

Post Febrile Course. — After the fever has subsided the clinical features of the post febrile course of this disease is dominated by the picture of paralysis. However certain other symptoms are evident and it is clear that the disease attacks to some extent other parts of the central nervous system than the anterior horn cells. Vasomotor disturbances

is between 25 and 100 cells but these figures do not represent rigid limits. Any number of cells have been reported from 0 up to 2,000. The presence of a high cell count, certainly anything over 1,000, will force the clinician to use his best judgment to differentiate this disease from meningitis. Although it is quite possible for such high cell counts to occur in poliomyelitis it is very unusual.

The cells are made up of variable proportions of polymorphonuclear cells and those of the lymphocyte series. In general it can be said that the proportion of polymorphonuclear cells is highest at the beginning of the disease and when the total cell count is high and gradually decreases so that lymphocytes predominate later. With an individual case however, which is never a statistical average, little help can be derived from any but gross variations. For instance the finding of over 90 per cent lymphocytes in several hundred cells in the first few days of illness should put one on guard against a diagnosis of poliomyelitis. There are no red cells in the spinal fluid of poliomyelitis victims except when they are produced by the trauma of the lumbar puncture.

The techniques of the clinical laboratories cannot be described here but certain common errors should be mentioned. The most important error is in the cell count. Cell differentiation can be made more satisfactorily in the counting chamber than by smear when the number of cells are small but red cells often are counted as lymphocytes. A count should always be made of the spinal fluid drawn into a white pipet after the stem has been filled to mark 1 with glacial acetic acid. The acid thoroughly shaken with the spinal fluid will hemolyze the erythrocytes and prevent confusion.

A sample of spinal fluid made bloody by the trauma of the tap should not be discarded as useless for study. A differential count of red and white cells may make it quite clear that an abnormal number of leukocytes are present.

New tubes for collecting the fluid and new glass slides for examination of smears should be used. Not infrequently old and dead bacteria remaining on glassware from previous use may be stained again and cause serious confusion.

Sugar Content — The sugar content of the spinal fluid usually is normal or increased somewhat above average.

Clinical Laboratory Findings in Poliomyelitis

The laboratory has very little to offer of aid in the diagnosis or understanding of the course of poliomyelitis except from a study of the spinal fluid. Poliomyelitis causes no change in the number or characteristics of red blood cells. Leucopenia is seen frequently in the human victim and in the experimental disease in monkeys. There is not enough consistency in this finding, however, to make the white count of any dependable aid in differential diagnosis.

The spinal fluid is of great importance in the diagnosis of this disease during the acute febrile stage. One can say with some emphasis that except in the paralytic stage the diagnosis of poliomyelitis depends upon a reasonable clinical suspicion leading to a lumbar puncture by a physician capable of properly examining and interpreting the spinal fluid. In spite of the importance of the spinal fluid examination, it must be emphasized at the outset that there are no changes in that fluid pathognomonic of poliomyelitis and many disease entities cause similar variations from normal.

Characteristics of Spinal Fluid

Globulin Content. — The globulin content is increased fairly consistently as demonstrated by the bedside laboratory tests. Statistical studies of this point[6] make it evident that the globulin is low at the early part of the disease, then rises fairly quickly and may be abnormally elevated for a considerable time after the end of the febrile period. It is quite possible that the globulin test will be negative at the onset of the illness. In the presence of an increase in the cell count of the spinal fluid the globulin test offers no additional information of value.

Cell Count. — The cell count furnishes the most valuable information to be obtained from the spinal fluid. An increase in cells (normal 0 to 8 ± per cu. mm.) appears within a few hours of the onset of fever and meningeal signs and usually persists during the febrile period. The cells may disappear, however, in as short a period as two days or occasionally may be found in small numbers for some days after temperature is normal. In the majority of cases the cell count is normal after the first week. The gross appearance of the spinal fluid in poliomyelitis is described as clear, ground glass or hazy in appearance. It is rarely cloudy. These descriptive terms should not be depended on and are unimportant as compared with an actual cell count. The usual range of the cell count

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lymphocytic meningitis or mumps encephalitis will produce a spinal fluid with such a high percentage of lymphocytes that one would consider it rather uncharacteristic of poliomyelitis. This is particularly true if the *cell count is high* since *counts of over 300 or 400 per cubic millimeter* consisting of 95 per cent or more lymphocytes must be very rare in poliomyelitis.

Syphilis. — There are no characteristics of the spinal fluid except the serological tests (Wassermann, Kahn, etc.) which distinguishes syphilis from poliomyelitis.

Multiple Peripheral Neuritis or Neuronitis. — In most cases only an increased globulin value is found although occasionally a small increase of white cells occur. In lead poisoning counts up to one or two hundred cells are sometimes found.

Poliomyelitis with a Normal Spinal Fluid

An important question asked is whether acute poliomyelitis can occur with no abnormalities in the spinal fluid. It seems reasonable to believe that this is so. Certainly we believe that there can be infection with the virus of poliomyelitis without involvement of the central nervous system but can the disease attack the central nervous system violently enough *to produce paralysis and still produce no changes in the spinal fluid*. This must be possible. However there often can be a simple explanation for the finding of a negative spinal fluid in the acute stage of the clinically recognizable disease. A negative spinal fluid can be obtained if lumbar puncture is done within a few hours of the onset of meningeal symptoms. It is thus quite possible to do a lumbar puncture too early as has been demonstrated many times in patients where a puncture done twelve hours later shows characteristic changes. It is quite possible also to do a lumbar puncture too late as in some instances the cells apparently disappear very early.

All cases cannot be so explained nevertheless and we must conclude that it is possible though rare to find a normal spinal fluid during the acute stage of poliomyelitis in a patient with evidence of paralysis. However great caution must be exercised in making a diagnosis of poliomyelitis under these circumstances even with paralysis apparent. At best it is often difficult to be sure of the diagnosis of this disease and with an absence of spinal fluid changes in the febrile stage a careful clinician must remain skeptical.

Differential Diagnosis of Spinal Fluid

It is important to discuss the differential diagnosis of poliomyelitis from other diseases of the central nervous system from the point of view of spinal fluid changes. A number of diseases produce changes similar enough to those of infantile paralysis to cause confusion.

Purulent Meningitis. — The spinal fluid of poliomyelitis shows a relatively low cell count. Any cell count over 1,000 or any cloudy fluid is due more likely to a purulent meningitis than to poliomyelitis. Here the level of the spinal fluid sugar may be of value, as in purulent meningitis the spinal fluid sugar usually is reduced, while in poliomyelitis it is increased or normal. No diagnosis should be considered established on this finding alone, however. Cultures and smears for demonstration of organisms always must be made carefully, whatever the presumptive diagnosis. It must be remembered that occasionally a purulent meningitis causes only a moderate increase in the cell count, especially very early in the disease, and in a late chronic course the cell count can be low and show a predominance of lymphocytes.

Tuberculous Meningitis. — This disease often causes confusion, particularly as poliomyelitis can occur with a stuporous sensorium quite like that of an encephalitis or tuberculous meningitis. The spinal fluids of poliomyelitis and tuberculous meningitis have the same characteristics except for the sugar content, which in tuberculous meningitis is reduced. Here again the sugar content, although very helpful, cannot be wholly relied on. The demonstration of tubercle bacilli in the spinal fluid is, of course, of crucial importance when it can be done.

Parameningeal Infection. — A collection of pus near the meninges, either a brain abscess or an extradural abscess such as those associated with mastoid infections, can produce a spinal fluid identical with that occurring in poliomyelitis.

Other Virus Infections of the Central Nervous System. — From study of the characteristics of spinal fluid in the clinical laboratory no feature can be detected which enable one to distinguish between poliomyelitis and a long series of other virus diseases which can affect the central nervous system. The encephalitis caused by measles, mumps, whooping cough, chicken pox and vaccination, as well as equine encephalitis, St. Louis encephalitis, choriomeningitis, etc., all show changes which fall within the same range of characteristics as poliomyelitis. Although statistical studies may show significant average differences between these diseases, in individual cases such figures are of no help. Occasionally

worker to detect Although such words as serious and crippling have little quantitative significance one can say with some accuracy that a quarter of all patients will have crippling paralysis greatly handicapping them in after life and that another quarter will have some obvious paralysis but one which will not be grossly incapacitating Such estimations as these are necessarily crude and the prognosis would undoubtedly be expressed differently by different observers

There seems no dependable clinical or laboratory feature which will enable the physician in the preparalytic stage to make a prognosis that is anything better than an interpretation of statistics However certain habits of the disease are of some aid

In the bulbar form of poliomyelitis the temperature is higher and more sustained However in these patients the evidence of paralysis occurs early and the elevation of temperature is not apt to precede paralytic symptoms by a great enough interval to aid in itself in prognosis

The intensity of the meningeal signs seems to have very little dependable relationship to the paralysis that will follow In fact it has been the opinion of some that patients with the most marked meningeal symptoms suffer the least paralysis

A fine tremor of one extremity exhibited in attempts to move it or to hold it extended sometimes precedes by a short period the paralysis of that muscle group but fine tremors in some nonparalytic patients are exhibited quite generally in all their muscles Muscle tenderness may either conceal or simulate a paralysis The presence of tenderness does not necessarily indicate that paralysis will occur

Danger of the occurrence of paralysis cannot be considered past as long as fever continues Usually the paralysis occurs in the second or third day of the febrile period but it may be the initiating symptom or may occur or be first recognized late The likelihood of paralysis certainly becomes less as the temperature drops although cases to the contrary are reported occasionally In general one can be pretty sure of freedom from further paralysis after the temperature has reached normal and has stayed so for a few hours Cases where late paralysis has been reported often can be explained by a failure to recognize a paralysis during the acute stage

Prognosis

Figures as to the fatality rate of poliomyelitis vary greatly.[7] In New York in 1916 the fatality rate was reported as 21.4 per cent in 4 15 cases, in 1930 it was 16.8 per cent in 660 cases, in 1931 it was only 8 per cent in over 2,000 cases, in 1940 the United States fatality rate was about 9 per cent. A reduction in reported fatality does not necessarily represent any lessening of the virulence of the disease but is in great part only evidence of an increasingly more astute diagnosis of the non-paralytic forms. Probably few deaths due to poliomyelitis are misdiagnosed, but a great many patients with a non-paralytic form of this disease are not diagnosed at all. The reduction in fatality rate as reported therefore represents an increased recognition of the milder forms of the disease and in general it is found that in years where a high incidence is reported and where physicians are on the alert, a low fatality rate is found.

Prognosis as Determined by a Study of Spinal Fluid

There is a natural tendency to believe that the higher the cell count in the spinal fluid the more severe will be the disease. This is not true. Although some statistical studies have been made which would seem to indicate a tendency the other way, there is no dependable relationship between mortality or severity of paralysis and the cell count which helps in an individual case. It is true that the severe and dangerous bulbar type of poliomyelitis commonly is associated with a low cell count, but ordinary spinal types also may show low counts. Extraordinarily high counts between 1,000 and 2,000 have occurred without any paralysis.

Prognosis of poliomyelitis can best be considered separately for the different periods of the disease at which the physician may first see the patient.

Prognosis in the Preparalytic Stage

During this period we are most concerned with the probability of the appearance of paralysis. This preparalytic stage may, in fact, be a part of a non-paralytic course. Of patients diagnosed in the febrile stage without paralysis about 70 per cent will acquire some form of paralysis. Probably not more than 50 per cent will have a paralysis of importance, the others merely some weakness that requires the observation of a skilled

prognosis but the bladder paralysis itself usually will disappear within a week or by the end of the febrile stage

CHARACTERISTICS OF ETIOLOGICAL AGENT

In 1909 Landsteiner and Popper[4] successfully produced poliomyelitis in monkeys by injecting into the monkeys brains an emulsion of the spinal cord of a human victim of that disease With the cords of these monkeys a disease with characteristic paralysis and pathology could be produced in turn in other monkeys The emulsified material was passed so successfully through filters with the elimination of bacteria but without loss of virulence that the determination of the etiological agent as a filterable virus soon was accepted by all except a few workers Improved technics in the preparation of the virus and in its purification and concentration have led to increasing success in the production of the disease in monkeys by other methods than the direct injection into the brain By physiochemical methods and filtration technics the material containing the virus has been more and more concentrated until a water clear product infective for monkeys in a dose as small as 0 0005 c c has been obtained

Certain characteristics of the virus may be mentioned briefly By ultrafiltration studies the size of the virus has been thought to be between 10 and 25 micra mu The virus is known to survive for a long time in sterile water in the dark and also in milk Substances like ether and glycerin seem harmless to the virus and therefore have been employed very profitably in the preservation of the virus and in its isolation from other materials Its thermal death point seems to be between 45 and 50 C for thirty minutes The virus seems to be destroyed or weakened by exposure to ultraviolet light and to be susceptible to destruction by certain oxidizing agents and fairly high concentrations of chlorine

Up until 1939 no other animal than the monkey has been dependably shown to be susceptible to the disease by any method of inoculation In 1939 a disease which seems characteristic of poliomyelitis was successfully produced for the first time in cotton rats by Armstrong[5, 12] The disease resulted from the inoculation of rats with virus from a human case of known poliomyelitis and the cords of these rats could be used in turn to infect other rats and monkeys After the virus was passed through a succession of rats it could infect mice also with a paralytic disease The successful inoculation of these small animals with a virus

Prognosis During the Acute Paralytic Stage

Here the prognosis for life will depend upon the occurrence or non occurrence of bulbar symptoms or of paralysis of the respiratory muscles Many cases with palatal and facial paralysis occur without there being more serious complications but difficulty in swallowing carries a greater risk It is difficult to get accurate figures to express this mathematically Certainly a large percentage of bulbar cases will recover A particularly high fever or rapid pulse must be considered especially serious Respiratory muscle paralysis varies from a barely discoverable weakness to complete loss of intercostals and diaphragm From experience with the respirator it is evident that considerable recovery usually takes place in most instances enough to allow breathing independent of a respirator

A dependable prognosis concerning the outcome of the paralysis found at this stage is impossible It is not wise to attempt a careful muscle examination of any quantitative value during the acute stage of the disease and muscle tenderness and meningeal symptoms are apt to make such an examination impossible anyway The paralysis that can be estimated during the acute stage of the disease or soon afterward is the worst that will occur and some degree of recovery almost invariably takes place Occasionally the recovery rate seems remarkable indeed and extraordinary cases are encountered where extensive paralysis seems quite to disappear Unfortunately this is not generally true, and as a whole the worse the detectable paralysis the worse the final crippling will be

The prognosis of certain types of paralysis is particularly good This is true of the paralysis of the soft palate and pharynx and the paralysis of the smooth muscles of the bladder and intestines Ultimate functional recovery in these groups of muscles usually is satisfactory Occasionally a nasal voice will persist indefinitely and in a few cases pharyngeal paralysis has been permanent In most instances that survive the acute stage however the patient will be able to swallow his own secretions by the end of five days or a week and to swallow food without great difficulty or without regurgitation through the nose if not by the end of the first week almost always by the end of the second or third Abdominal distension with constipation disappears with the end of the febrile stage Bladder paralysis causing urinary retention almost invariably is associated with extensive paralysis of both legs and because of that carries a bad

and an outline of the views regarding pathogenesis most generally held at this time will be given

The important morphological changes produced in the body are found in the central nervous system On gross examination of the tissues at the autopsy table the spinal cord or medulla are swollen and when transected the surfaces bulge outward due to an intense edema the swelling of the gray matter being particularly evident Throughout the gray matter minute red spots due to congested blood vessels may appear There may be evident some mild inflammatory reaction in the meninges and a variable degree of cerebral edema In patients seen long after the acute stage the spinal cord atrophy and particularly the absence of the large motor cells has been mentioned already This may be so extreme that in patients who have died a few weeks after the acute stage of the disease with paralysis so extensive that they had been kept alive only by the action of the modern respirator actual necrosis of large areas in the anterior horns is seen where a column of gelatinous material or in some instances actual cavitation can be traced up and down the cord

Although the gross pathological changes found in victims of infantile paralysis are limited almost entirely to the central nervous system other signs of disease can be found There is a variable degree of swelling and engorgement of the lymphatic tissues especially evident in the Peyer's patches of the intestinal tract There are variable changes found in the lungs congestion bronchopneumonia atelectasis with hemorrhagic and serous transudate which are apparently nonspecific and secondary to the mechanism of death which is almost always associated with grave disturbances in respiration

Histological examination reveals abnormalities in many parts of the central nervous system which vary greatly in intensity but the most striking changes are limited to the cord and medulla It is well to concentrate attention separately first on the supporting or interstitial structures of the cord and second on the large ganglion cells As will be discussed later the question as to the relationship of these two processes has been a matter of great controversy and on the decision as to which is primary depends many questions of etiology pathogenesis and therapy

An intense inflammatory reaction in the supporting or interstitial structures dominates the microscopic picture The congestive process is most marked by far in the anterior horns of the gray matter particularly around the blood vessels which are often intensely engorged It is apparent that most of the red specks that were seen on a gross examination

of poliomyelitis has not proved of as great value to research as was first hoped for, since the susceptibility of mice and rats is only to certain specific strains of the virus which are not widespread in the human disease. These animals therefore cannot be used as test tubes for the dependable detection of the distribution of the virus in epidemics.

It is evident that poliomyelitis exists in different strains[14] and that these strains possess different potentialities for causing the disease in animals. So far only a few strains of virus has been shown capable of infecting rats and mice. It has been shown that the rodent-adapted strain of virus is neutralized by many human sera containing poliomyelitis antibodies obtained from scattered cases in this country but not by all sera. These demonstrable variations in the characteristics of the poliomyelitis virus still further complicate the study of the disease.

Pathogenesis

Early in the history of poliomyelitis the morphological changes in the central nervous system were studied in an effort to understand the origin of the symptoms. Very accurate observations were reported many years ago[1-18] and it was realized quickly, as indeed it had been surmised previously, that paralysis, the essential symptom of the disease, was caused by damage to the anterior horn cells of the spinal cord. The earliest studies were on the bodies of patients who died at considerable intervals after the onset of the disease and who had suffered extensive paralysis. In these the spinal cord was atrophied and shrunken, and later histological studies showed that there was a marked diminution or complete absence of the large motor cells of the anterior horns. These changes still seem the most significant in understanding the final effect of poliomyelitis.

As soon as it became evident that the disease was caused by an ultramicroscopic agent, a filterable virus[5], the study of the disease experimentally produced in the monkey was followed with intense interest. Much of the knowledge of the pathological changes occurring in the acute stage was therefore derived from artificially infected monkeys, and it was obvious that conclusions from these studies could not safely be applied directly to the human disease. It has become apparent, however, that the histological changes produced by the disease are the same in monkeys and in man, although there may be great variation in the areas of maximum damage and in the distribution of the virus.

The essential pathological changes will be summarized only briefly,

cortex It should be pointed out with a good deal of emphasis that none of these pathological changes that have just been described can be considered in themselves pathognomonic of the disease entity poliomyelitis The perivascular infiltration changes in the great motor cells in the meninges and in the interstitial tissues all can be found paralleled individually or in combination in other diseases of the central nervous system such as for instance epidemic encephalitis The feature which may be considered characteristic of poliomyelitis is only the distribution of these lesions so characteristically in the anterior horn of the spinal cord or in the motor area of the medulla

There has been always great difficulty in interpreting the sequence of events taking place in a diseased cord from the symptoms that a patient demonstrates It is important to realize that the morphological changes seen in the central nervous system at death do not clearly explain all the symptoms shown in life This is true in the human as well as the monkey victims of the disease The extent of the pathological changes always is far greater than the clinical evidences of palsies would have indicated It is apparent that morphologically we cannot tell the difference between functioning and nonfunctioning nerve cells between sick but recoverable cells and those fatally injured which will go on to lysis The pathological changes do not explain the sudden and somewhat dramatic appearance of paralysis which is seen occasionally Disease processes in other parts of the nervous system than the anterior horn cells are very clearly evident even though they do not occur as frequently nor appear to be as intense It has been hard to correlate the presence or absence of other symptoms than paralysis with what can be seen morphologically It has seemed to some difficult to explain the pain of the disease by changes in the ganglion cells of sensory nerves since this pain is relieved so greatly by local treatment of tender muscles but it is probably more to be wondered at that more symptoms do not occur that there is not more evidence of paresthesia or anesthesia and of upper motor neuron defects and that there is no evidence of permanent neurological residue other than that of a flaccid paralysis

Study of the morphological effects of the experimentally produced disease in monkeys has been depended on to clarify the sequence of events taking place in the central nervous system during the disease Two schools of thought have existed for many years and many experimental studies have been stimulated and directed by the rather long drawn out controversy regarding the chronology of the morbid process

are due to erythrocytes contained within the lumen of the vessel. There is evidence of only a moderate degree of extravasation of blood and no evidence of thrombus formation and by inference therefore no evidence of damage to the intima. The interstitial tissues quite generally are edematous and infiltrated by leucocytes mostly of a small round cell type. Around the blood vessels there is a particularly intense infiltration with lymphocytes. This perivascular infiltration often is so marked as to form collar like areas of cells which make it easy to believe that actual obstruction to the flow of blood or at least to diffusion of oxygen, might exist. Most of this perivascular infiltration is around the venules and not around the arterioles.

Although this picture of edema infiltration with white cells and perivascular cuffing with lymphocytes is by far the most marked in the cord and medulla similar changes may be seen but to far less a degree in the interstitial tissues of the brain. The pia itself shows also some vascular engorgement not only over the cord but also over the brain. The bulges of the cord in the cervical region and in the lumbar region are, however by far the most consistently and intensely affected.

Changes in the minute structures of the ganglion cells although inconspicuous amidst the dominating intensity of the interstitial reaction have seemed to be of especial importance because of our knowledge of their function. The appearance of the ganglion cells varies according to the stage of the disease. As has been mentioned before exact knowledge of the sequence of events has been determined almost wholly from experimental lesions in monkeys. Similar results have been seen consistently in the human disease however and there is every reason to believe that the cellular changes are identical. It seems evident that a series of events takes place in the ganglion cells preceding from lysis of the chromatic material to general lysis of the whole cell coagulative necrosis and neuronophagia with final disappearance. The earliest change in the large motor cells is a diffuse granular clouding of the cytoplasm apparently due to the disintegration of the bodies of Nissl. Some swollen ganglion cells are seen with clear cytoplasm that takes no stain. Still others appear shrunken isochromatic with nuclei no longer visible. Around these large and injured ganglion cells there appear at times other cells whose origin is disputed which seem to have a phagocytic action.

The pathological process in the ganglion cells as in the interstitial tissues is not limited to the anterior horn of the cord or to the medulla but similar changes in kind although usually not in intensity can be seen in other parts of the central nervous system particularly in the motor

The engorgement of the Peyer's patches in the gut in the acute disease early directed the attention of students to the intestinal tract as a portal of entry. It has long been suspected by some and particularly energetically taught by Toomey[1] that the intestinal mucosa was the entrance point. In the last few years the finding of virus in the stools of human patients suffering from poliomyelitis as well as sometimes in sewage of hospitals and cities[3,4] make it highly probable that the intestinal tract is at least one entrance point of the virus in human infection. The virus is found more readily in the intestinal tract than in the pharyngeal secretions of human subjects. Just the opposite is generally true in monkeys, although certain ones, the Cynomolgus monkey for instance, is particularly susceptible to oral infections[5,6]. The technique of administration of the virus by mouth, of course, does not always clearly distinguish between absorption through the intestinal tract or through the upper respiratory tract.

Certain other possibilities must still be considered. It is quite possible with certain strains of virus in certain monkeys to cause infection through the skin. This probably has been brought about in man where certain cases of poliomyelitis have occurred following attempts to cause active immunity by the injection of a vaccine.

The incidence of cases of poliomyelitis following a tonsillectomy has been discussed in other sections. The coincidence of the two conditions is altogether too great to be explained by chance and seems to offer a very good example of local trauma opening a portal for entry.

Transmission Through the Body

Once the virus has entered the body, it becomes of great concern to consider how it is transmitted through the body to the central nervous system. The blood, lymphatic system or the nerves themselves have been considered reasonably possible pathways. The engorgement of the Peyser's patches and the swelling of other lymphatic tissues of the body has been offered as evidence to implicate the lymphatic system. The cellular reaction in the spinal fluid and the evidence of pial congestion has seemed to point toward the cerebral spinal fluid system as a pathway for the movement of the virus to the central nervous system or at least from one part of the central nervous system to another. We cannot go into the details of this problem, but it now seems very probable that the virus reaches the cord and brain by way of the axones of nerves[3]. It has

By one school it is believed that the primary initiating abnormality is in the anterior horn cells the great motor cells themselves, that here the virus first causes disease, and that from here the symptoms first arise Other changes are explained as secondary or at least associated changes The second school of thought has believed that the important and first lesion is the interstitial congestion and particularly the perivascular infiltration of lymphocytes that thereby circulation is obstructed and that the great motor nerves are damaged by subsequent anemia

The path of conjecture and surmise resulting from morphological observations has been long and devious and sometimes has turned back on itself and any thorough understanding of our present conception can only be obtained by a historical review of investigations for the past sixty years This is impossible to do here with any thoroughness and we can only outline the conception most generally held at this time

An understanding of the sequence of events that occur in the spinal cord requires a conception of how the virus itself enters the body, how it is transmitted through the body to the central nervous system and how it passes through the central nervous system itself

Portal of Entry

A consideration of the portal of entry of the virus could be undertaken as profitably in a discussion of epidemiology but studies of this problem necessarily have been linked closely with experimental pathology It is obvious that the most successful technic for the infection of monkeys with poliomyelitis by intracerebral inoculation is wholly artificial and can have no relationship to the human disease It has long been apparent that monkeys could be successfully and rather consistently inoculated with poliomyelitis virus through the mucous membranes of the nose[1] and pathological studies would indicate rather clearly that the virus can enter the central nervous system of Macacus rhesus by way of the olfactory bulb[18, 19] From this for a long time it was concluded pretty generally that human beings were infected the same way particularly as virus has been demonstrated in the nasal secretions of victims of poliomyelitis However very thorough studies[9] on fatal human cases of poliomyelitis have shown no lesion in the olfactory bulbs similar to those found in monkeys and no virus was demonstrated in the olfactory bulbs although it has been demonstrated repeatedly in the olfactory bulbs of monkeys infected by the nasal route

of the virus on the nerve cell and may through their effect on circulation explain sudden changes for the worse

Evidence of Immunity and Susceptibility

Evidence of immunity or susceptibility to poliomyelitis lies in (1) the demonstration of antibodies in the blood and ( ) observations regarding the incidence of the disease

Antibodies

As long ago as 1910 the blood serum of both monkey and human convalescents from poliomyelitis was shown to possess certain protective properties that is to contain antibodies[24 3] It is important to understand the way such antibodies were demonstrated After emulsions of the spinal cord of victims of poliomyelitis were injected directly into the brain of monkeys these monkeys were observed to come down fairly consistently with a disease entity characteristic of poliomyelitis When convalescent serum obtained first from monkeys and later from human subjects was mixed in vitro with these cord suspensions for a short time and then the combination of virus and convalescent serum injected into the brain the monkeys failed to come down with the disease

For the last three decades these basic experiments have been repeated many times and constitute the only way of detecting and quantitating antibodies to poliomyelitis In spite of susceptibility of rats and mice to certain specific strains of the virus the monkey has been the only animal susceptible to enough strains to be generally useful for detecting both virus and antibodies It can easily be understood how great the restriction to investigation must be when these expensive biological test tubes are the only means for the acquisition of this type of information

Demonstration of these antibodies in human serum has seemed in the past of tremendous importance not only in regard to the understanding of epidemics but as a possible means of developing effective methods of prevention or therapy However since many varieties of virus and specific antibodies are now known to exist and since most of the experiments in the past have used only one strain of the virus and that one passed many times through monkeys and have therefore detected only one type of antibodies the information obtained in the past has

been established that the virus in contact with an exposed nerve slightly injured can cause poliomyelitis in the subject[4] When a nerve is frozen temporarily at one point and a short time allowed for recovery the ability of the nerve to transmit the virus when exposed to it at a point distal to the area that had been frozen is lost By histological study it has been shown that by the freezing only the axone of the nerve is damaged for long the other structures of the nerve and the surrounding tissues quickly recover and if they offer a possible pathway should be able to transmit the virus as well as before Studies tracing the path of the virus in the central nervous system by the morphological changes produced by it and by actual demonstration of the virus makes it probable that it infiltrates the entire nervous system rather rapidly by way of nerve axones and not by the myelin sheaths of nerves or through lymphatic or interstitial tissues

A very plausible explanation of the inflammation of the meninges and interstitial tissues has been offered by experiments which seem almost crucial concerning this point Motor nerve cells in one section of the brain have been caused to atrophy by destruction of its nerve connections with another part of the brain When such regions of the brain devoid of motor cells are infected directly with an emulsion containing the virus no local inflammatory process is seen although in other parts of the brain where the motor cells are still intact characteristic changes of the interstitial tissue occur These experiments as well as others make it highly probable that the perivascular infiltration with lymphocytes and all the changes in the interstitial tissues of the cord and meninges are secondary processes which can be brought about only subsequent to damage and destruction of the large motor cells for which the virus has an apparent specific affinity As has been mentioned before all the changes seen histologically in poliomyelitis are different only in distribution from those caused by other diseases affecting the central nervous system

It is certainly premature to conclude that even if the virus does attack the anterior horn cells first the changes occurring there are brought about only by the action of the virus and that the intense reactions seen in the interstitial tissues are quite inconsequential and do not in themselves cause damage Although the onset of paralysis is not always abrupt often it has occurred so suddenly that thrombotic and embolic processes were surmised originally as an explanation It is very possible that the secondary interstitial changes themselves do aggravate the effects

still that there is no dependable relation between the level of humoral antibodies and the susceptibility of the nervous system to the nerve axon transmitted virus

Evidence of Immunity from Clinical Studies

There are a number of observations which would demonstrate a constitutional tendency or natural immunity and susceptibility to poliomyelitis Some evidence of an hereditary susceptibility to poliomyelitis has been described in studies of the incidence of poliomyelitis in certain family histories[31] Draper has long believed that certain features in body build and face are associated more commonly with poliomyelitis than others and he describes what to him is a typical patient with a rather broad face epicanthus folds incisor teeth somewhat separated as representing a type peculiarly susceptible to infection This work although interesting is viewed with skepticism by many

There is no evidence of racial immunity or susceptibility that can be distinguished from the effects of climate and geographical distribution The greater incidence of poliomyelitis in temperate zones has been considered well established though recently some have felt that this has been apparent rather than real because of faulty observation in areas with less well developed medical services Certainly the southern states of this country recently have suffered as severely as the northern states

The statement is often made that poliomyelitis attacks pretty and attractive children Since most children are pretty and attractive it is hard to attach much value to such observation

There is little evidence that the general health of the individual is a factor in susceptibility Certainly it has long been noted that the victims of poliomyelitis are commonly well nourished big children without definite preceding illness[25] Although we are prone to believe that resistance to disease in general is diminished by poor health this tendency is certainly not evident in poliomyelitis From our experiences with diseases of bacterial origin it would seem also that nutrition itself should be a factor in the incidence of poliomyelities and that poor nutrition should lead to increased susceptibility The evidence would point to an opposite effect and there is a general belief derived particularly from the study of the disease *in animals that virus maladies actually are more* likely to attack healthy individuals than the under nurished So far there is little evidence that any specific vitamin lack leads to increased susceptibility

been very incomplete and must all be re-evaluated. Although the usefulness of past studies of the incidence of antibodies is limited for this reason, it is worthwhile to summarize it briefly. After the first demonstration of the existence of antibodies it was soon determined that not only those convalescent from poliomyelitis but also adults never known to have had the disease could be shown to have antibodies in their blood. Using the standard strain of virus, it has been shown that 75 to 80 per cent of adults possess such demonstrable antibodies[30, 31]. It is evident likewise that many infants at birth have antibodies which soon disappear later to be reacquired. The proportion of individuals who possess antibodies increases in different age groups as maturation takes place[7, 8].

In this discussion we have used the word antibodies instead of immunity, and it is possible that the presence of these antibodies has little relation to general immunity. It has been determined, for instance, that both in monkeys and in human victims of the disease there is a great delay in the appearance of antibodies after infection and that in fact the appearance of antibodies after infection is not consistent. It is known that convalescent monkeys who do not develop demonstrable antibodies are in many instances still refractory to a second inoculation with the virus. Both human beings and monkeys have been noted to be infected with the virus at a time when antibodies were present in their blood. There is further evidence that the incidence of dependably observed second infections with poliomyelitis is, after all, as great as might be expected from the probability of the disease in any population group[32]. These facts, plus the failure of attempts to use convalescent serum either for prevention or for therapy of the disease, have cast a reasonable doubt about the protective values of antibodies. It has been questioned whether infection with the disease produces any general dependable immunity.

Our present knowledge that there are multiple strains of viruses antigenically specific opens up this whole subject for re-evaluation and may be the basis for an explanation of the failure of the therapeutic value of convalescent serum. It is quite possible that if antibodies to specific strains obtained from individual patients were studied, quite different results would be found[7, 8]. Recent epidemics of American troops stationed in Asiatic areas where rather intense outbreaks occurred in an area where the local population had no incidence of the disease points towards a difference in the immunological protective mechanisms that have developed in the two races.

We should not be too hopeful, however, that here lies the only explanation of the failure of convalescent serum. It seems quite possible

still that there is no dependable relation between the level of humoral antibodies and the susceptibility of the nervous system to the nerve axon transmitted virus

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The statement is often made that poliomyelitis attacks pretty and attractive children Since most children are pretty and attractive it is hard to attach much value to such observation

There is little evidence that the general health of the individual is a factor in susceptibility Certainly it has long been noted that the victims of poliomyelitis are commonly well nourished big children without definite preceding illness[6] Although we are prone to believe that resistance to disease in general is diminished by poor health this tendency is certainly not evident in poliomyelitis From our experiences with diseases of bacterial origin it would seem also that nutrition itself should be a factor in the incidence of poliomyelities and that poor nutrition should lead to increased susceptibility The evidence would point to an opposite effect and there is a general belief derived particularly from the study of the disease in animals that virus maladies actually are more likely to attack healthy individuals than the under nurished So far there is little evidence that any specific vitamin lack leads to increased susceptibility

been very incomplete and must all be re-evaluated. Although the usefulness of past studies of the incidence of antibodies is limited for this reason, it is worthwhile to summarize it briefly. After the first demonstration of the existence of antibodies it was soon determined that not only those convalescent from poliomyelitis but also adults never known to have had the disease could be shown to have antibodies in their blood. Using the standard strain of virus, it has been shown that 75 to 80 per cent of adults possess such demonstrable antibodies[30, 31]. It is evident likewise that many infants at birth have antibodies which soon disappear, later to be reacquired. The proportion of individuals who possess antibodies increases in different age groups as maturation takes place[1, 43].

In this discussion we have used the word antibodies instead of immunity, and it is possible that the presence of these antibodies has little relation to general immunity. It has been determined, for instance, that both in monkeys and in human victims of the disease there is a great delay in the appearance of antibodies after infection and that in fact the appearance of antibodies after infection is not consistent. It is known that convalescent monkeys who do not develop demonstrable antibodies are in many instances still refractory to a second inoculation with the virus. Both human beings and monkeys have been noted to be infected with the virus at a time when antibodies were present in their blood. There is further evidence that the incidence of dependably observed second infections with poliomyelitis is, after all, as great as might be expected from the probability of the disease in any population group[33]. These facts, plus the failure of attempts to use convalescent serum either for prevention or for therapy of the disease, have cast a reasonable doubt about the protective values of antibodies. It has been questioned whether infection with the disease produces any general dependable immunity.

Our present knowledge that there are multiple strains of viruses antigenically specific opens up this whole subject for re-evaluation and may be the basis for an explanation of the failure of the therapeutic value of convalescent serum. It is quite possible that if antibodies to specific strains obtained from individual patients were studied, quite different results would be found[7, 6]. Recent epidemics of American troops stationed in Asiatic areas, where rather intense outbreaks occurred in an area where the local population had no incidence of the disease[3], points towards a difference in the immunological protective mechanisms that have developed in the two races.

We should not be too hopeful, however, that here lies the only explanation of the failure of convalescent serum. It seems quite possible

with meningeal symptoms or with spinal fluid changes are now seen commonly but are less dependably reported For the past fifteen or twenty years it has been believed by many that the virus of poliomyelitis can cause disease without even meningeal symptoms so called abortive poliomyelitis a condition impossible to diagnose accurately Reports concerning the incidence of the disease have varied widely due to different criteria of diagnosis and varying acuity of reporting physicians

In epidemics attack rates varying from very low figures to between one and three cases per 1 000 of population usually are reported If abortive cases could be diagnosed much higher rates might of course be found although there is a great yearly variation An average incidence in the United States of about 5 000 cases a year occurred from 1920 to 1930 but since then the number has increased to nearer 10 000 and in the last few years the incidence has been over 20 000 It is undetermined how much of this increase is due to better reporting and more accurate observations consequent to the greatly increased public interest in poliomyelitis This number still is not large considering the incidence of other diseases but if one considers that thousands of permanent cripples are left each year the importance of the disease becomes clear

It is obvious that reports of abortive cases must be open to a great deal of question since no dependable technics exist for their accurate diagnosis However such observations as have been made suggest that in epidemic areas patients having a febrile but ill defined illness which may be due to poliomyelitis may be found eight times as often as those having definite illness of the central nervous system which can be diagnosed clearly as poliomyelitis

Geographical Incidence — Although sporadic cases have been reported all over the world the greatest incidence is in temperate zones The greatest epidemics have been seen in the northern half of the United States in Sweden and in Australia though recently the southern states of this country have suffered severe outbreaks

Seasonal Incidence — The curve of incidence starts in midsummer and reaches its peak in late summer and early fall In an epidemic area in the northern part of the United States usually a few cases appear in June rather definite evidence of an epidemic is apparent in July with a peak incidence of the disease in August and September followed by a few cases occurring as late as November In the Southern States the curve of the epidemic shows a tendency to start and end one or two months earlier In Australia the seasonal incidence is the same as in North America the peak of the epidemic being also in the late summer but the

Recent studies offer some evidence that injury to the central nervous system may bring about diminished susceptibility. It has been shown by animal experiments in which a peripheral nerve has been cut, that after a few days the motor cells supplying axis cylinders to that nerve becomes refractory to the poliomyelitis virus[2, 27]. It has been shown also that monkeys recently infected with lymphocytic choriomeningitis are more resistant to inoculation with the poliomyelitis virus[28].

Certain injuries seem definitely to diminish resistance. It has seemed very clearly established that the tissue injury caused by tonsillectomy when this operation has been carried out where poliomyelitis is prevalent produces a definitely increased risk of that disease. The incidence of poliomyelitis and more important the bulbar type of the disease occurring one or two weeks after tonsillectomy is greater than ordinary probabilities would explain. An associated observation is that a large percentage of children with acute poliomyelitis show evidences of a pharyngitis or tonsillitis.

There is some evidence of a much more than chance coincidence of dysentery and poliomyelitis or of poliomyelitis following recent dysentery.

Epidemiology

Although the characteristics of epidemics of poliomyelitis have been the subject of many studies and information is being constantly acquired concerning the mode of spread of the virus, we do not have yet any clear idea how to control this disease.

Poliomyelitis is widespread and has been known to occur at all seasons of the year and in practically all parts of the world and to affect people at all ages. Although it probably is a disease of some antiquity there is some evidence that there has been a change in its characteristics in the past 50 or 60 years so that while previously it occurred mostly sporadically, it is seen now most commonly in distinct epidemics. It is hard to believe that epidemics such as we see now could have been missed in the past years even though our techniques for diagnosis are now far better.

Incidence of Poliomyelitis

Reports of the incidence of poliomyelitis in years past were first wholly reports of incidence of paralysis. Cases without paralysis but

expensive procedure must be carried out wholly on monkeys of different species Some success has been obtained by the use of mice and rats as has already been noted but since these animals seem to be susceptible only to a few specific strains they are not useful for studying the spread of the disease in human epidemics

Distribution of Virus — The virus has been found in pharyngeal secretions but rarely in carefully taken nasal secretions of human victims of the disease It rarely is found in pharyngeal secretions after the first two or three days of the acute febrile stage It has been demonstrated in stools in a little more than 10 per cent of convalescent patients as late as at the end of the second month after onset[9] It has been demonstrated occasionally to persist many months so that speculation arises as to how the virus lives and propagates itself during this period The virus has been found in the sewage of hospitals and even in the discharge of cities where immense dilution must have taken place[53, 54] Virus has been detected in the stools of people who have not suffered from the disease in a recognizable form

The problem to be solved is whether the virus is spread through human contact patients or carriers by some insect vector or by means of water and food The corollary problem is whether the entrance point to the body is through the respiratory system or through the gastro intestinal tract Although it seems quite conclusive that the virus itself can be widespread at least in epidemic times it is not clear that it is indiscriminately widespread and there is much evidence that the intensity of the spread is a function of the closeness of group contacts

When several members of one family become ill with poliomyelitis it is generally true that all come down with the illness at about the same time or within a few days as if they had a common source of infection In several small communities epidemics have been noted explosive in nature where the onset of all cases occurred within a few days On the other hand occasionally very definite intervals of one to two weeks occur between successive patients in a family indicating fairly clearly that one individual is the source of infection to others Intimate human contact although obviously a possible factor and one that seems to explain some small outbreaks certainly does not adequately explain large epidemics For instance it is pointed out that epidemics occur in this country at a time when children are not in school or at least the height of the epidemic occurs before school opens in the fall

In spite of the evidence pointing to human contact as a means of

time in the year of seasons themselves is, of course, the reverse of that occurring at the same time in the northern hemisphere

It has been reported that the number of cases during epidemics is greatest in hot and dry weather Rather vaguely established impressions about changes in the incidences of the disease from day to day due to changes in the weather are prevalent The validity of such observations should be questioned and if the incubation period actually is as long as usually is reported one to two weeks it is obvious that daily variations of the weather cannot have a very clearly defined effect

Age Incidence — The common name of this disease infantile paralysis suggests an age incidence which at present is misleading There is evidence that years ago the common name was more accurate than seems to be so at present The disease is now very rare under six months of age and infrequent under one year Some thirty or forty years ago in urban centers 80 to 90 per cent of the cases were reported in children under five years of age In recent years however in North American Swedish and Australian cities the greatest incidence is in the five to nine year group and in some parts of the United States as much as one third of all paralyzed patients are older or adolescent children[58]

In the past it was noted that a higher incidence amongst adults occurred in rural areas than in urban areas The explanation offered for this difference in age incidence has been the slower development of immunity in rural areas consequent to less opportunity for exposure to the virus During the last few years this difference between urban and rural age incidence of the disease seems to be less

Method of Spread of the Disease

Up to recently our knowledge of the spread of poliomyelitis has been almost wholly dependent on our ability to trace from patient to patient the disease as it became clinically apparent It is obvious that ability to demonstrate the presence of the virus itself offers an extremely valuable technic for supplementing the study of any epidemic particularly when it is apparent that the virus is far more widespread than clinical paralytic cases would indicate The virus can be detected only by inoculation of a susceptible animal with suspected material and by the subsequent demonstration of the disease in the inoculated animal to be certain this procedure must be supported further by the demonstration that tissues of these animals can transmit the disease to still others This rather

Where such infection did take place frequently one could dispute the possibility that the respiratory tract was not infected during the process of the experiment However past work was done usually on the Rhesus monkey with virus which had been passed for many years through the brains of these monkeys Recent demonstrations that oral administration of strains of virus of recent human origin could produce paralytic polio myelitis fairly consistently in chimpanzees and particularly in the Cynomolgus monkey without the olfactory pathway or the respiratory tract being involved resolves to a certain extent the controversy

In summary it can be said that although we seem nearer a solution of the problem than before the exact mode of spread of poliomyelitis and the pathway of entrance into the body by the virus is not surely determined The major argument seems to be whether contact is through a respiratory or gastrointestinal transmission The pharynx where the virus has frequently been found is of course as much a part of the upper respiratory tract as a part of the upper alimentary tract As a whole the evidence points to the gastrointestinal route as a common portal of entry however the virus may be spread from patient to patient, although there may well be several portals of entrance

Contagiousness

The contagiousness of poliomyelitis is of course a function both of the intensity of the spread of the etiological agent and of susceptibility of immunity in contact individuals Studies in recent years make it far clearer than it used to be that there is a rather intense local spread of the virus around infected individuals even though the virus can also be found rather widespread

The degree of contagiousness of poliomyelitis can perhaps be best expressed by a comparison with familiar contagious diseases although the comparison cannot be made in any exact way It is clear that polio myelitis is far less contagious for instance than measles and chicken pox It is probable that immunity without clinical infection is far more wide spread Poliomyelitis can be considered less contagious than scarlet fever although that disease has been much milder with less intense epidemics in recent years Where it used to be considered rare to have more than one case of poliomyelitis in a family recent years have changed that impression greatly and multiple infections are discovered quite com monly in families as one patient with paralysis has directed more skilful

transmission of poliomyelitis several epidemics have seemed to implicate fairly clearly a food supply It has been pointed out that there was an increased incidence of the disease in cities along the shores of bodies of water and that the disease could be traced along water courses However this certainty is not apparent in all epidemics and when it is apparent it is not at all clear that the findings are statistically significant It has been thought that the incidence of the disease is greater amongst children who have been swimming but it has not been clearly established that the history of swimming in victims is any greater than in the brothers and sisters who are not ill

The seasonal incidence of poliomyelitis has suggested to many that an insect vector is responsible Many small outbreaks are highly suggestive of the action of an insect vector The virus has now been detected repeatedly by different observers in mixed collections of flies and other insects in the epidemic areas[60, 61] However there is still no certain evidence that the disease actually is transmitted through these insect vectors

In spite of the finding of virus in sewage in communities where poliomyelitis is prevalent in flies that could be contaminated by sewage and in stools of individual patients and their close associates the case distribution of poliomyelitis in epidemics is not similar to that generally found in epidemics of enteric infections Poliomyelitis is not a disease of filth or more common in areas with poor sewage disposal Epidemics have occurred with greatest frequency and severity in the very countries where sanitation and hygiene have made the greatest advances We see great epidemics in large cities in this country where in equally large cities in the same latitude in China for instance no such epidemics are recorded in spite of the presence there of well trained physicians who would have detected it

Finding the virus in stools certainly does not prove that the disease is transmitted through sewage It has not been determined for instance that the measles virus is not also in the stools of patients with measles although we do not suspect that the virus of measles is so transmitted Finding the virus on flies and other insects does not by any means settle the mode of transmission as through food It has been established in recent years beyond doubt that experimental oral infection can be readily achieved in monkeys [ ] In past years controversy existed on this point and there were few reported successes of infection of monkeys except by the olfactory pathway Only occasional incidences of infection through the gastrointestinal tract seemed to have been accomplished

Quarantine Quarantine of unproven value Modified quarantine restricting the movements of intimate contacts for 7 to 14 days may be desirable under certain circumstances

Isolation in bed of all children with fever pending diagnosis

Protection of children so far as practicable against unnecessary contacts with persons other than their usual associates

Avoidance of unnecessary travelling and visiting especially of children during a high prevalence of the infection

Patients with acute poliomyelitis or presumed to have acute poliomyelitis are admissible to general hospitals provided that appropriate isolation precautions are used No special isolation or pest facilities are necessary

The isolation procedures used for the care of acute poliomyelitis patients are similar to technics used in the hospital care of other communicable diseases

In order that the best possible facilities be used for the care of poliomyelitis patients may be sent from their own home communities to a hospital in another community Available evidence indicates that such importation of poliomyelitis patients into a hospital in a community where poliomyelitis is not prevalent does not affect the incidence of the disease in the hospital community

Public and private schools should not be closed during an outbreak of poliomyelitis nor their opening delayed except

1 Schools to which children are transported in buses in widely separated areas may be delayed in opening

Boarding schools may delay opening if an outbreak of poliomyelitis exists in the area where the school is located and if children are thus prevented from coming into the area from regions where the disease is not prevalent

Summer camps should be open as usual if there is no outbreak of poliomyelities in the community in which the camp is located In case of an outbreak in a summer camp it is recommended that the following procedure be instituted

1 Retention of children s staff at the camp for 14 days after the last contacts with a case or until the usual closing date of camp

Modified and supervised activity to prevent excessive exercise and undue mixed activities of children with suspicious signs and symptoms

3 Discontinue admission of new children to camps

It is recommended that health officers do not take action to close

medical attention to other members If we are going to accept any minor illness not otherwise explained, occurring in a family where recognizable poliomyelitis exists as being also a manifestation of 'abortive' or subclinical poliomyelitis it might be considered that the disease does approach in contagiousness such a disease as scarlet fever However, we have of course no good evidence to justify such suppositions although it is tempting to do so as an easy explanation of the widespread development of immune bodies Recently the intense outbreaks in the American troops in the Pacific with a high incidence of the disease in communities where natives were not infected throws further light on the relationship of immunity to contagiousness

Patients with poliomyelitis in many large cities are sent to isolation hospitals but they have been also accepted for many years in general hospitals with rather simple isolation technics without more evidence of cross infection than one would find with pneumonia However, in both diseases although the evidence of spread of the disease is slight we must admit that the spread of the etiological agent may be far greater Although carelessness can never be excused the safety with which experience has shown hospitalization can be carried out certainly does not justify exclusion of the poliomyelitis patient from any hospital prepared to take care of acute illnesses The facilities of a contagious hospital or the old fashioned 'pest house' are certainly not necessary

Public Health Recommendations

The theoretical basis for Public Health recommendations during an epidemic of poliomyelitis has been discussed Such facts as are known furnish a meager basis for decisive or effective public health measures Nevertheless as a guide to local community health officers some general outline of recommended practices in the control of poliomyelitis have been agreed upon by a sub committee on Communicable Diseases of the Committee on Research and Standards of the American Public Health Association Following are excerpts from these recommendations

Isolation of patients For one week from date of onset or duration of fever if longer Concurrent disinfection Nose and throat discharges and feces are infectious and should be disposed of as quickly and safely as possible Articles soiled therewith should be promptly disinfected

Terminal disinfection None

Quarantine Quarantine of unproven value Modified quarantine restricting the movements of intimate contacts for 7 to 14 days may be desirable under certain circumstances

Isolation in bed of all children with fever pending diagnosis

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2 Modified and supervised activity to prevent excessive exercise and undue mixed activities of children with suspicious signs and symptoms
3 Discontinue admission of new children to camps

It is recommended that health officers do not take action to close

or prevent the operation of places of recreation or amusement such as fairs circuses theatres swimming pools or beaches provided that they are properly operated However the attendance of children at such places should be discouraged

Criteria for Diagnosis

There is no practicably available laboratory technic for the certain establishment of the diagnosis of poliomyelitis either at the time of the acute disease or later At necropsy it is possible by animal inoculations with an emulsion of the cord of the victim of the disease to prove the diagnosis by the same technic that Landsteiner used in the original determination of the etiology of poliomyelitis The demonstration of antibodies in the convalescent patient is neither practicable nor dependable Even if the expense of a monkey protection experiment with the patient's serum is undertaken one experiment does not certainly establish the presence or absence of antibodies nor if it did would that finding have any necessary relation to the disease being studied

There is nothing in the examination of the spinal fluid by itself that can lead to a positive diagnosis of poliomyelitis Spinal fluid changes can be considered typical of or compatible with poliomyelitis but there are many other diseases which can produce identical changes In the absence of paralysis the diagnosis must be established without final and specific proof and on a basis of clinical judgment Paralysis when it does occur is fairly characteristic but probably no type of paralysis can be considered pathognomonic All this should not imply that a diagnosis of poliomyelitis based on a characteristic clinical picture plus a compatible spinal fluid is not as dependable as the diagnoses we must accept in many other diseases

Differential Diagnosis

The diagnosis of poliomyelitis may be said to depend on a sound clinical suspicion justifying a lumbar puncture by a physician able to properly examine and interpret the spinal fluid Inaccuracies in the diagnosis of poliomyelitis occur for opposite reasons depending on whether a recognized epidemic is or is not present In times of epidemic a great many diseases will be thought to resemble poliomyelitis because the doctor is on the alert for such a condition or has it suggested to him by worried families At these times therefore many false diagnoses of poliomyelitis are made and many unnecessary lumbar punctures are

done In non epidemic times on the other hand the occasional case of poliomyelitis is apt to be mistaken for some other condition and no lumbar puncture done or proper diagnosis made Faced with a single patient one should guard against being influenced by disease frequency in the community

Although the age incidence is well known to be greatest in childhood the disease can occur at any period of life so that usually little help can be gained from consideration of age However poliomyelitis is rare under eight months and the diagnosis must be made with great caution in early infancy The physician inexperienced with children is prone to make a wrong diagnosis in the first months of life where syphilis or birth injuries are common

The conditions which in certain aspects resemble poliomyelitis and cause worry and confusion to the physician are many and may vary from the stubbed and tender toe of the toddler to a brain tumor and include almost all acute infections Any complete list would be uninstructive from its lack of emphasis

The manner in which a clinician arrives at a diagnosis of poliomyelitis is differentiated from other pathological processes will depend on the symptoms first presented and these will vary greatly at different stages of the disease Differential diagnosis will be considered first in respect to the disease as it presents itself without paralysis and second in the disease when the symptom of paralysis is dominant as in the following outline In most puzzling cases resort to spinal fluid examination is necessary Discussion of the spinal fluid will be found in the section on laboratory data and will not be repeated Differential diagnosis will be discussed under the following schema

SCHEMA I

I Diagnosis in the Febrile Non paralytic Disease
II Diagnosis in the Disease with Paralysis
  A Paralysis of Extremities and Trunk
    (Pseudo-paralysis)
    (Actual Paralysis)
  B Bulbar Paralysis
III Diagnosis in the Encephalitic Type of Disease

Differential diagnosis during the first hump of the disease having the so called dromedary course need hardly be considered since it is

or prevent the operation of places of recreation or amusement such as fairs circuses theatres swimming pools or beaches provided that they are properly operated However the attendance of children at such places should be discouraged

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The spinal fluid usually offers the best differential points since the type of cell in these is predominantly lymphocytic as discussed in the section on laboratory findings Often differential diagnosis cannot be made between these diseases and non paralytic poliomyelitis

Para meningeal Abscesses — A brain abscess or an extradural abscess may produce meningeal irritation with fever headache and stiff neck and back The spinal fluid may be sterile with low cell count and similar to that of poliomyelitis Differential diagnosis will depend on the detection of other neurological findings produced by the brain abscess or in the detection of the extradural abscess Otitis media with some evidence of acute or chronic mastoiditis should be carefully looked for

Meningismus — This term generally is used arbitrarily for symptoms of increased intercranial pressure plus stiff neck and back occurring with the rise of temperature at the onset of any acute infection not of the central nervous system The syndrome is particularly common in children The added symptom of a convulsion is frequent in young children and babies and when this occurs poliomyelitis should be excluded easily When meningism without a convulsion occurs therefore any acute infection may be confused with poliomyelitis and the differentiation depends on the detection of the infection The most common infections producing meningism are pneumonia pyelitis typhoid and dysentery but any acute infection may be initiated by these symptoms These need not be discussed here in detail If the diagnosis is not made clear immediately by physical examination and study of the urine and stool a lumbar puncture must be done not only to exclude poliomyelitis but even more important to detect a purulent and specifically remediable meningitis

Rheumatic Fever — Rheumatic fever sometimes may be confused with this stage of infantile paralysis In rheumatic fever we find headaches and joint pains which might be interpreted in children especially as muscle pains Swelling and redness of the joints frequently are not very evident in children The sensorium is clear When there is some spinal involvement in rheumatic fever a stiff neck and back may make the picture strikingly similar It must be determined if possible whether the tenderness is in the muscles or in the joints Associated erythema multiforme rheumatic nodules signs of a typical cardiac lesion usually clarify the situation but occasionally spinal fluid examination will be thought necessary

Upper Respiratory Tract Infection — Influenza or the beginning of an upper respiratory infection may be particularly puzzling There again headache fever and in children vomiting are common General aches

impossible to make the diagnosis at that time. One can suspect poliomyelitis only because cases closely associated with the patient have been recognized. The spinal fluid will be negative, there will be no characteristic neurological signs, and one can only wait for developments to identify the illness.

Diagnosis in Non-paralytic Disease or Preparalytic Stage

The practical approach to the diagnosis when no paralysis is present lies in evaluating the clinical picture to the point where a spinal fluid examination seems necessary. All of the important symptoms will be included in the following: headache, fever, vomiting, stiff neck and back, pain in neck and back or pain more generally. Headache, fever and vomiting are common to a great many acute infections. The problem lies, therefore, in the differentiation of acute infections with meningeal symptoms with or without the additional symptom of local or generalized pains, and the diseases to be considered are included mostly by the terms meningitis or meningismus.

Meningitis.—The stiff neck and back in poliomyelitis is different from that in meningitis as in most instances the resistance to flexion or the discomfort on flexion is higher in the spine. This is not as important in differentiation, however, as the state of the sensorium of the patient and his response to attempts to examine him. The patient with meningitis very likely will be stuporous and hard to arouse, may be in coma, and even if not probably will ignore requests to sit up in bed or to bend the head forward. He may well have had a convulsion which should itself exclude poliomyelitis. In poliomyelitis we would expect a rather alert, anxious and usually fairly intelligently cooperating patient. However, mild cases of meningitis without much toxicity occur, and an encephalitic or unconscious state approaching that of acute meningitis occurs in poliomyelitis, so that the correct diagnosis can only be determined by study of the spinal fluid. This differentiation is discussed further under encephalitic types of the disease.

Mumps and Lymphocytic Meningitis.—Mumps and so called lymphocytic meningitis, serous meningitis or chorio-encephalitis quite characteristically produce a picture of fever, headache, stiff neck and back with clear sensorium and changes in the spinal fluid all quite similar to poliomyelitis. Mumps may be differentiated from infantile paralysis from the presence of parotitis either in the patient or in a close contact

sidered a necessary symptom although this is absent frequently The characteristic angulation of the costal-chondral junction, the history of a faulty vitamin intake and the age of the patient should make the diagnosis clear The demonstration that the leg is not actually paralyzed usually can be made by a proper pain stimulus X-rays of the legs properly interpreted makes the correct diagnosis Lumbar puncture should never be necessary

Syphilis in the same manner as scurvy may produce a picture simulating localized paralysis In infants a syphilitic osteomyelitis can cause a pseudo-paralysis which has been misdiagnosed as poliomyelitis The age of the patient should prevent such a mistake even before Wassermann tests or x ray of the long bones establish the diagnosis The differentiation of true neurological lesions due to syphilis will be discussed later

Trauma —Small children frequently hurt themselves causing green stick fractures sprains muscle hematomata or even inconspicuous skin injuries which make them limp or refuse to use an arm or leg Since the injury may be unreported and occur without being observed by any older person and since cooperation during muscle examination is poor confusion of worrying parents and their physician is great Even a sliver of wood in a toe of a two year old during an epidemic may raise the question of poliomyelitis When the injury is associated with a febrile respiratory infection or involves the neck or back and simulates meningeal irritation a diagnosis may be very difficult to make without resorting to a lumbar puncture or waiting for time to clarify the situation

Pseudo paralysis Due to Chorea —Sydenham s chorea sometimes is confused with poliomyelitis when it occurs as so-called hemichorea One arm alone may appear quite helpless and flaccid and only careful observation may make it clear that some evidence of choreiform motion is present in the extremities or face and that on painful stimulus the suspected paralyzed arm can in fact be moved and usually quite violently

Differentiation of Actual Paralyses of the Trunk and Extremities — Exclusion of Upper Motor Neuron Conditions —Having determined that a paralysis is real and not simulated the next step should be to determine whether it is a spastic or flaccid paralysis that is whether the lesion is in an upper motor neuron or due to damage to the lower motor neuron Ordinarily differentiation is easy but quite commonly the appearance of an upper motor neuron lesion is for a few hours or even a few days that of a flaccid paralysis and it is quite difficult to determine the basic physiological mechanism Evidence of increased intracranial pressure of increased reflexes in other extremities or of eye ground changes often

and pains may make one think of poliomyelitis Evidence of sore throat may be scanty or certainly not more pronounced than is found frequently in poliomyelitis A stiff back of very mild degree often can be seen when one is particularly looking for it The heart is somewhat rapid as in poliomyelitis

Muscle Tenderness —Localized muscle tenderness is a common symptom of poliomyelitis and is not necessarily associated with paralysis Occasionally therefore a case of infantile paralysis is considered osteomyelitis or arthritis or vice versa Physical examination study of the white blood count or the presence of meningeal signs usually clarify the situation otherwise a lumbar puncture will be necessary

Diagnosis in Disease with Signs of Paralysis

Where paralysis or the semblance of it is apparent this symptom becomes the leading point in the diagnostic attack Paralysis in poliomyelitis may be encountered first in the acute febrile meningeal stage or as an isolated symptom after the febrile period is past The approach to the differentiation of the spinal palsies should be made by orderly steps, first determination of the actual existence of paralysis by differentiation of pseudo-paralysis from real paralysis second, differentiation from upper motor neuron disease If it is determined that an actual flaccid lower motor neuron paralysis exists then further differentiation should be considered between diseases attacking other parts of the cord as well as the motor cells and lastly between lesions of the peripheral nerves and trunks of the motor nerve cells The symptomatology of the bulbar and respiratory paralysis need to be considered separately from paralyses of the trunk and extremities

Differentiation of Paralysis of Trunk and Extremities —*Pseudo paralysis* —One group of diseases confused with poliomyelitis is that which produces tenderness of extremities so that a patient s unwillingness to contract a muscle because of pain may be interpreted as paralysis This problem is of course most commonly encountered with infants and children *Osteomyelitis* has been mentioned already

Scurvy in infants in epidemic times not infrequently is called poliomyelitis The child is observed not to move its legs or not to move one leg, and the evident pain is explained as the muscle tenderness of poliomyelitis Fever in scurvy is common the disease is seldom thought of by most physicians and when it is considered bleeding gums are con

In general as distinct from poliomyelitis the paralysis of these diseases is insidious in onset is more diffuse in appearance obviously progresses over a period of days or weeks and final recovery is complete

Post diphtheritic paralysis is the most common entity in this group and in many features is like the others The paralysis after diphtheria is diffuse and often only partial This is quite strikingly different from the typical picture of poliomyelitis where one expects to see a fairly sharply localized rather easily identified paralysis such as of the biceps of some of the gluteal muscles of the deltoid or of the anterior tibial group These paralyses may be complete or only partial but the point to be noted is that they are fairly sharply localized On the other hand if one studies the history of patients with diphtheritic paralysis one has the impression that there is first generalized weakness before the term paralysis is used Motion of the leg exists in all directions but is carried out quite feebly Ultimately in post diphtheritic paralysis both legs are apt to be extensively paralyzed the arms far less often than the legs and very rarely alone without associated paralysis of the legs The knee kicks are lost very early in diphtheria while in poliomyelitis usually they are exaggerated in the early part of the disease Certainly if the knee kicks are present it is very unlikely that the disease is post diphtheritic paralysis

Lead paralysis in adults characteristically involves first the small muscles of the hands and feet The absence of the story of an acute illness and the usual attempts to make a diagnosis of lead poisoning from study of the blood the appearance of gums or in growing children from x ray evidence of deposits in the ends of the long bones should clarify the diagnosis quickly However children with lead poisoning occasionally are found being treated for poliomyelitis in orthopedic clinics

Syphilis – The pseudo paralysis due to syphilitic osteomyelitis in small infants has been mentioned Syphilis also is seen to cause a sudden flaccid paralysis In poliomyelitis a story of a preceding acute illness with characteristic symptoms usually is found but not always obtained Syphilitic meningitis can offer a confusingly similar story Study of the Wassermann or other serum reaction of syphilis in the blood and spinal fluid is necessary to distinguish the two conditions where the poliomyelitis story is not typical and this procedure should be routine in any case of paralysis

Bulbar or Respiratory Muscle Paralysis – The symptoms produced by paralysis may be misinterpreted and the existence of paralysis be unrecognized This is particularly likely when respiratory distress or difficulty in swallowing occurs

make a differentiation clear. A history of a convulsion often is helpful since the flaccid stage of an upper motor neuron lesion is quite common after a convulsion. It should be emphasized here, although it has been stated already before, that a convulsion is not part of the picture of acute poliomyelitis and an apparent flaccid paralysis which has followed a recognized convulsion should never be diagnosed as due to poliomyelitis. It is not necessary to list here the causes of spastic paralysis or upper motor neuron lesion.

Exclusion of Other than Motor Cell Lesions in the Cord. —Faced with a flaccid paralysis, one should determine first whether or not there are true and dependable changes in sensation. If there is clearly a loss of sensation to touch, to pain, of position sense, poliomyelitis can be ruled out quickly. Certainly only in rare questionable instances does poliomyelitis cause symptoms due to damage to other parts of the central nervous system than the motor cells. The only common exception to this statement may be the pain of poliomyelitis, the cause of which has not been determined surely, but if neurological in nature must lie in some other lesion than in the anterior horn cells. The picture of a transsection of the cord itself is quite quickly distinguished from poliomyelitis by the most gross form of neurological examination.

Exclusion of Peripheral Nerve Lesions. —Making the distinction between a peripheral nerve lesion and a motor cell lesion is the crux of the differentiation between poliomyelitis and other diseases causing lower motor neuron paralysis. When all of a nerve trunk is so involved as to prevent its functioning, evidence of sensory nerve distributions may rule out poliomyelitis fairly quickly. When only the motor part of a nerve trunk is involved, knowledge of the distribution of a nerve is helpful in differential diagnosis. Obviously all the muscles controlled by the nerve trunk will be affected. It is rather characteristic for a peripheral nerve lesion that extensively involves the arms or legs to bring about a paralysis of the fingers and toes as well as of the great muscles. Poliomyelitis, on the other hand, since it strikes the anterior horn cells themselves, frequently causes a nearly complete paralysis of the whole extremity but leaves the toes or fingers unparalyzed.

A number of diseases occur which cause lower motor neuron palsies and all of these conditions cannot be discussed separately. The nomenclature is confused, but multiple neuritis, peripheral neuritis or postinfectious neuritis or neuronitis are favorite terms. The coincidence or history of immediately preceding infection with the virus of measles, mumps, chicken pox or vaccinia often makes the etiological agent clear.

paralysis are lost early while in the acute stage of poliomyelitis during which palatal paralysis is encountered the knee kicks are apt to be exaggerated if changed at all from normal In diphtheria ocular palsies commonly are associated with swallowing difficulty while in poliomyelitis this is rare and facial palsies are more common Other paralyses if they exist may help in the differentiation A spinal fluid examination usually will settle the matter unless the paralysis is of some duration

Cerebral Embolus — Occasionally during epidemics of poliomyelitis a cerebral embolus causing stertorous breathing with unswallowed secretions obstructing inspiration may be called poliomyelitis

Bulbar Palsies of the Degenerative Type — More frequently in adults than in small children differentiation has to be made between bulbar poliomyelitis and the pharyngeal paralysis that occurs in degenerative bulbar palsies The poliomyelitis picture is that of an acute disease and the history alone usually is sufficient to differentiate the two A negative spinal fluid is found rarely in pharyngeal paralysis due to poliomyelitis since that paralysis if the patient survives is of relatively short duration

Brain tumors occasionally may simulate the pharyngeal paralysis of poliomyelitis Other neurological symptoms plus the evidence of chronic increased intracranial pressure usually quickly differentiate the two

Retro pharyngeal abscess has been misdiagnosed as bulbar poliomyelitis in epidemic times and the opposite mistake has been made even more commonly at other seasons In both instances there is difficulty in swallowing and in a small child the gurgling type of respiration easily may cause confusion Children with retropharyngeal paralysis resist anterior flexion of the neck It should be recalled that at least half the cases of acute poliomyelitis show some evidence of pharyngeal or tonsillar inflammation and sometimes the evidence of an upper respiratory infection is quite marked Careful palpation of the throat and if that is negative lumbar puncture should quickly make the correct diagnosis clear

Differential Diagnosis of the Encephalitic Type of Poliomyelitis

Some patients with poliomyelitis present themselves with changes in sensorium suggesting encephalitis While ordinarily the patient with poliomyelitis is alert at least when aroused is intelligent and quite conscious of what is going on occasionally we see a patient excessively dulled and stuporous lying in coma The encephalitic sensorium quite commonly is associated with the bulbar type of paralysis but may occur

Pneumonia — Although it would seem to differ greatly from poliomyelitis pneumonia can be confused with poliomyelitis Pneumonia with little dyspnea because of the frequently associated meningeal symptoms in an epidemic may be considered to be poliomyelitis On the other hand poliomyelitis with intercostal or diaphragmatic paralysis may cause respiratory difficulty with a striking difference in excursion of one side of the chest from the other This with the obvious dyspnea may lead the careless observer to diagnose the most usual condition which leads to such disturbances in breathing pneumonia or respiratory obstruction It is rare that any such mistakes can be explained by anything but superficial and careless observation Almost always intercostal paralysis is associated with paralysis of the arms which can be detected easily No abnormal breath sounds should be heard in poliomyelitis

Difficulty in Swallowing — Confusion in diagnosis is quite common when the presenting symptom offered by a patient is that of inability to swallow The existence of pharyngeal paralysis often is not recognized The victims of infantile paralysis when young may not themselves at first understand their own difficulty When medical aid is sought belatedly, or the disease is rapid in course the patient may present himself first in a state of coma or semicoma with noisy interrupted breathing and with obvious and marked respiratory difficulty The condition has been confused with *overwhelming pneumonia* or *sepsis*, the noisy stertorous breathing suggesting that often seen in patients in extremis A key to the proper diagnosis should be apparent particularly if any consciousness on the patient s part can be detected as soon as the noisy breathing is recognized as due to unswallowed secretions in the throat The breathing characteristically is grossly irregular with inspiration frequently interrupted by attempts at sudden expiration or by ineffective efforts to cough Usually the patients themselves unless indeed far gone and near death will show symptoms of great apprehension or terror When the patient is old enough to recognize his difficulty early in the course of his trouble or when it is evident from watching a patient try to drink some water that there is inability to swallow a *foreign body* causing obstruction to the esophagus is apt to be considered and more than one child with pharyngeal paralysis unfortunately has been esophagoscoped

Diphtheria has to be considered when palatal paralysis is recognized The presenting symptom is nasal speech and nasal regurgitation on attempts to swallow The absence of diphtheritic membrane in the throat of course does not rule out this condition The knee jerks in diphtheritic

preventing a spread of the disease Certainly most epidemics run a course which seems to be self regulated and self limited apparently not influenced by public health procedures General community warnings against aggregations of people during epidemic times usually are given schools are closed or not opened and parents are urged to protect their children from fatigue and to consult their physicians early The number of cases of poliomyelitis following one or two weeks after tonsillectomy although actually small is great enough to be significant and is more than chance association Most pediatricians agree that the operation should be avoided when poliomyelitis is epidemic

Plans for isolation of patients in homes and hospitals usually have followed the techniques for non enteric infections Our latest observations of the widespread distribution of the virus in oral secretions and in sewage make it improbable that such efforts have been effective Probably more attention should be paid to the value of enteric precautions although it is apparent that the virus is widespread and is excreted by many people not ill or known to have been ill with the disease

Protection by Specific Active Immunization — Various attempts to develop a vaccine for the widespread immunization of people in epidemic areas have been made[40, 41, 4] These attempts have been based upon hopeful experimental work with animals However in general it has been proved that a vaccine attenuated enough to be safe is ineffective Experiments in monkeys which seem to show definite protective action have not been carried out without evidence of actual transmission of the disease itself In one extensive and tragic human experiment it seems probable that actual infection of a number of individuals was induced Since no means exist for determining by any test the susceptibility of an individual to the disease and since no accurate determination of exposure risks of individuals is possible even in small epidemics, it is evident that many hundreds of people would have to be treated with a vaccine to prevent one case of the disease from occurring Even if an effective and safe vaccine was developed a tremendous problem is presented by the difficulties of immunizing a large group of people in an epidemic area and of completing the injections and allowing time for immunization to occur while it still might be helpful and before the epidemic itself dies a natural death

Protection by Nasal Sprays — Experiments on monkeys showed that, if the olfactory nerve ending in the mucous membranes of the nose were destroyed by coagulating agents those so treated were protected from nasal injections of virus which caused poliomyelitis in the controls[43, 44, 4]

as well in cases with spinal paralysis or no paralysis at all Here the differential diagnosis lies between poliomyelitis, tuberculous meningitis and all the diseases classified under the term encephalitis Tuberculous meningitis is distinguished by the finding of other evidences of tuberculosis, especially by chest x-ray, by a positive tuberculin test and by distinguishing characteristics in the spinal fluid as has been described under that section Characteristic of tuberculosis of the central nervous system is the marked disturbance of respiration with long periods of apnea There is nothing pathognomonic in this picture but frequent deep sighing irregularly intermittent hyperpnea and apnea are seen far more commonly in tuberculosis than in encephalitis or poliomyelitis The history is of course very helpful in differentiation as the symptomatology of tuberculous meningitis develops gradually Whether the virus of poliomyelitis can cause an encephalitis with convulsions and residual upper motor neuron defects has been disputed Apparent encephalitis has been reported frequently during epidemics of poliomyelitis Our knowledge of variations of virus strain is very incomplete but at present there seems no justification for inclusion of diseases with such widely different symptomatology under the diagnosis of poliomyelitis even though the seasonal incidence is similar Convulsions and early and deep coma associated with upper motor neuron defect should rule against a diagnosis of poliomyelitis

Prevention and Treatment

No effective method for the prevention of this disease and no effective specific treatment of it after it has occurred has yet been discovered Discussion of this subject cannot of course be left with this categorical and pessimistic statement and mention should be made of the most hopeful procedures that have been carried out even though they are generally accepted as ineffective

Prevention

Attempts to prevent the spread of the disease have been made always in any recognized epidemic Various types and degrees of isolation techniques have been insisted upon by different health authorities There is no certain evidence that isolation has been effective or ineffective in

of paralysis no consideration could be given to the number of patients who did not have any paralysis and who therefore escaped observation but who were also obviously untreated When finally studies were made treating only alternate patients who were diagnosed as being in the pre paralytic stage no significant difference in the degree of paralysis was observed[3 4]

It was already clear from experiments with monkeys that no amount of convalescent serum was effective in preventing the extension of the disease in monkeys if given at the period of the disease when human treatment was necessarily given that is during the preparalytic meningeal stage More studies on the relationship of the presence of antibodies to the incidence of the disease makes it even less likely than convalescent serum would be effective even if it could be administered long before the central nervous system were involved

Treatment by Procedures Directed Toward Controlling the Circulation in the Cord

As discussed on the section on pathology a striking feature in this disease has been the perivascular infiltration of the cord with lymphocytes From this it was argued that the damage to the nerve cells themselves was due to anoxia or some other effect resulting from choking off the circulation to the anterior horn cells Accordingly therapeutic efforts were directed towards preventing or dispersing the collection of cells around blood vessels of the cord and towards reducing the edema of the brain and the cord Repeated or continuous drainage of spinal fluid has been recommended Hypertonic fluids were administered intravenously to reduce the edema Adrenalin was given intraspinally Hypotonic solutions were administered parenterally and large amounts of water were given by mouth while continuous spinal drainage was maintained The hypotonic solution therapy was based upon the observation that with diffuse production and drainage of spinal fluid the cell count changed from a polymorphonuclear to a lymphocytic character and it was argued from this that the collection of white cells around the vessels of the anterior part of the cord were being washed out by the flow of fluid

All these methods have had eloquent advocates Striking results were seen to follow in numerous instances However different observers have had widely different experiences with the same techniques Treatment

As so frequently happens in this disease public interest and excitement stimulated the early application of the result of these experiments to human beings It was hoped that if similar treatments on the noses of people in an epidemic area were carried out that the spread of the disease might be stopped It is of course evident that the method of infections of the monkeys was highly artificial that the state of the mucous membranes in the nose would have to be kept the same throughout the duration of an epidemic and that subsequent to healing fissures might conceivably make an individual more rather than less susceptible However several extensive experiments were carried out with definitely discouraging results[45, 4] No evidence of protection was demonstrated Since the role of the intestinal tract as a possible portal of entrance of the virus has become better known and a few thorough studies of the olfactory bulbs in fatal cases of poliomyelitis showed no evidence of the virus, the nasal prophylaxis treatment seems even more illogical

Specific Treatment with Human "Immune" Serum

The demonstrations of antibodies in the blood of human convalescents from the disease was recognized early as offering a possible mode of treatment Virus first mixed with human convalescent serum and then injected into a monkey s brain failed to cause a disease although the injection of the virus without the serum did so Inoculation of a monkey with human convalescent serum a few hours before or after nasal injection with a potent virus also was observed to protect monkeys occasionally, although by no means consistently It was learned later that there was a variable amount of antibodies demonstrable by the same technique in the blood of adults not known to have had the disease Accordingly extensive experiments were carried out with pooled convalescent serum and human adult serum given to patients in the early preparalytic stage of poliomyelitis Hundreds of patients were so treated and the results furnished a classic example of the danger of any studies without proper controls It was found that a great deal less paralysis occurred in patients treated with convalescent serum in the preparalytic stage of poliomyelitis than was found in patients who were not so treated[48, 49] Year after year the patients who were not given the serum were those discovered and diagnosed after paralysis had occurred and because paralysis had occurred and finally it became obvious to all that these patients were no fair or proper controls In the untreated group recognized only because

of paralysis no consideration could be given to the number of patients who did not have any paralysis and who therefore escaped observation but who were also obviously untreated When finally studies were made treating only alternate patients who were diagnosed as being in the preparalytic stage no significant difference in the degree of paralysis was observed[9, 1]

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with both hypotonic and hypertonic solutions have received equally enthusiastic support No well controlled studies of any of these methods of therapy have been presented, and we are forced to look on all these efforts as rather desperate attempts to "do something" To a very great extent the conception that the virus first attacks the great motor cells and that the edema and perivascular infiltration is secondary destroys the logic of such treatments It is still quite possible, however that the secondary interstitial changes may exaggerate the damage produced by the virus and attempts at a more critical evaluation of these methods of therapy still are justifiable

General Treatment

Rest — Recent evidence[61] strongly suggests that the value of rest in the preparalytic and the early paralytic stage of poliomyelitis may be considerably greater than we are apt to consider it in other diseases and that activity or rest may actually make the difference between permanent destruction and temporary incapacity of certain nerve cells The evidence supporting this idea is derived from the observation that the patients with the worst paralysis give a more consistent story of continuous activity sometimes violent during the very early hours or days of the disease Some experimental evidence on monkeys has been presented also Although the matter cannot be said to be absolutely proved it seems justified to make every effort to insist that absolute rest be carried out at the first sign of illness due to poliomyelitis or in epidemics at the first symptom of any undiagnosed febrile illness

Fluids — Fear is often expressed of giving too much fluid particularly parenterally to patients suffering from edema of the medulla The possible effects of fluids on the processes in the spinal cord have been discussed already A reasonable program should make a compromise between overhydration and dehydration and a moderate amount of fluid with consideration for the patient's fever and sweating and most of all his comfort should be allowed

Skin — These patients sweat profusely and are partially immobilized both by tenderness and actual paralysis This should cause us to direct nursing attention particularly to the care of skin Dry clothes and alcohol rubs should be attended to assiduously Care of the skin will be complicated further by the application of hot wet packs to tender muscle groups

Comfort — Poliomyelitis patients suffer a great deal The treatment of muscle tenderness with heat packs will be mentioned under the treatment of paralysis The physician must be particularly concerned in directing the nursing of infants and small children who may be handled by their attendants without any proper realization of the degree of pain that is caused Attempts to evaluate paralysis by the doctor to change the diapers by the nurse and other routine procedures should be carried out with the greatest gentleness

Intestinal Stasis — Disturbance in the function of the intestine and paralysis of the bladder need particular attention during the acute stage of the disease Constipation is marked in many patients and probably is at least partially due to a disturbance of peristalsis brought about by the disease Intestinal stasis is temporary and lasts only a few days but abdominal pain due to the constipation should be relieved by small enemas gently administered

Urinary Retention — Bladder paralysis also will be temporary Relief may be obtained by catheterization after it has been demonstrated that the patient cannot void spontaneously The risk of catheterization is justified by the marked urinary retention and the pain which would occur otherwise Usually two or three catheterizations will be enough to carry the patient over this phase of his disease

Treatment of Paralysis Leading to Respiratory Failure

The manner in which poliomyelitis may lead to respiratory failure has been described already and the treatment of these conditions is dependent upon a clear understanding of the underlying mechanism With any patient showing any evidence of respiratory disturbance the problem lies in finding out how much the difficulty is due to paralysis of intercostal and diaphragmatic muscles how much is due to paralysis of the pharynx with unswallowed secretions interfering with respiration and how much is due to disturbance in the respiratory and vasomotor centers in the medulla Discussion of this diagnostic problem has been given earlier

When respiratory failure is due to intercostal and diaphragmatic paralysis artificial respiration is the only treatment The device invented by Drinker and now manufactured in different forms seems to have met the immediate problem adequately The details of this specialized treatment cannot be discussed here These machines seem wholly effective

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a tendency for patients with bulbar poliomyelitis to vomit that this method of feeding is dangerous It is wisest to give orally neither food nor fluids to patients with pharyngeal paralysis until their temperature is normal and in fact until they complain of hunger An attack of vomiting is associated with nausea and the nausea brings about increased pharyngeal secretions which may produce as much distress or danger as the vomitus itself Salt water and carbohydrates in adequate amounts can be administered parenterally and by rectum to keep the patient in a good state of hydration and free of ketosis for the duration of the acute stage of disease Both excessive thirst and thick tenacious pharyngeal *secretions difficult to remove can be prevented by giving adequate* parenteral fluids Continuous intravenous infusions are at times indicated but the dosage of fluids must be carefully regulated because of the danger of increasing cerebral edema by over hydration A compromise between unrestricted fluid administration and a restriction which might lead to signs of dehydration seems wisest

Postural drainage frequently results in a surprising amount of mucus and saliva flowing from the mouth The postural drainage should be boldly carried out The patient should be tilted head down at an angle of as much as thirty degrees and during attacks of choking if these are not prevented the head should be put even lower Frequently the patient is aided by being kept on his face It may be necessary to maintain his position in bed by fixation of the ankles to the elevated foot of the bed

In treating any patient with pharyngeal paralysis aspiration of the secretions from the throat frequently is of life saving value and suitable apparatus for accomplishing this should always be at hand Effective emergency suction apparatus can be devised from a vacuum cleaner with a bottle water trap that could be made up in any laboratory A source of suction in an emergency can be an attendant s own lungs with a water trap intervening Electrically driven apparatus is available in most hospitals and must be wherever these patients are to be cared for but the amount of suction that they can develop is so great that careful attention should be given to the danger of traumatizing the mucous membranes if the machine is not carefully regulated Aspiration should be carried out as little as possible to keep the patient comfortable as in certain excitable patients it may irritate the pharynx increase the fear and apprehension of the patient and so increase the production of mucus In some *patients such great relief is afforded* by aspiration that they request it and can sometimes carry it out themselves In children a great deal of tact and reassurance is necessary and the suction device should be introduced

in doing what might be expected of them for these specific paralyses but they will not help the interference of respiration which is secondary to pharyngeal paralysis or to dysfunction of the medullary centers controlling respiration The respirator will produce a tidal flow of air in any patient who relaxes so that the machine can have its effect who has no obstruction and whose airways are unobstructed One could consider the use of the respirator for respiratory paralysis as desirable, not only to save life in extremely paralyzed patients who would otherwise die but to give rest to those partially paralyzed patients with only slight dyspnea The relief to these moderately paralyzed patients is often far more striking than would be expected Not infrequently symptoms of mental confusion due to anoxia or accumulative fatigue may be relieved, when the patient is given respirator treatment, in spite of the fact that it was not obvious that the muscles of respiration were severely paralyzed A justification for the use of the respirator in severely stricken patients rests wholly upon the possibility that the respirator muscles will improve If improvement could not take place to an extent allowing the patient eventually to become independent of such a device and if the respirator treatment only led to a persistence of this tragic situation its use could hardly have been justified However no absolutely bad prognosis for recovery can be so certainly made that withholding the use of the respirator at the time when its use is first indicated can be justified Some recovery almost always occurs and occasionally very remarkable return of function is evident

Probably much more good can be done in the aid of patients with respiratory difficulty due to pharyngeal paralysis since the prognosis for this paralysis is always good, if life can be maintained throughout the acute course of the disease Although this condition as well as that with respiratory muscle paralysis is often confused with medullary respiratory center disturbance and any two or all three can co exist in the same patient we must consider therapy for this specific condition the diagnosis of which has been discussed already The principal therapy for these patients should be to keep the pharynx free from food vomitus and secretions and if this cannot be effected to provide an airway by means of tracheotomy The steps to be considered therefore are prevention of vomiting the use of postural drainage aspiration of the throat and finally tracheotomy with the use of oxygen where indicated

It seems easy in patients with pharyngeal paralysis to feed by gavage or to attempt to put small amounts of fluid into the mouth in the hope that it will finally find its way into the stomach However there is such

to aspiration and postural drainage can give one a good idea of the need for tracheotomy before one gets into great difficulties

One should demand that a patient under the more conservative method of postural drainage and aspiration should be able to get such relief that he can relax and go to sleep If he cannot one can be sure that the condition will get progressively worse and that fatigue will greatly prejudice the chances of a successful outcome Sometimes it is extremely difficult to determine whether the irregular respirations are due to pharyngeal secretions or to damage to the respirator centers themselves in the brain stem A tracheotomy here does not seem logical However it is often difficult to make a clear distinction as to which is causing the symptoms we see and if uncertainty exists after careful observation a tracheotomy is justified even though the patient may die soon after Rarely adductor paralysis in the larynx may contribute to or cause respiratory difficulty and such a situation is clearly an indication for tracheotomy

The use of oxygen is entirely logical whenever there is an interference with pulmonary ventilation The use of oxygen by a closed tent should not be resorted to however in such a way that other and more direct attempts to relieve respiratory difficulty cannot be carried out or that constant observation is prevented Many patients have died by neglect in oxygen tents simply because they were not carefully observed there and the clinician relied too much upon the administration of oxygen as a panacea for respiratory difficulty It must also be clearly understood that oxygen administration may increase the oxygen in the alveolar air but cannot aid in the excretion of carbon dioxide in respiratory difficulty and therefore may not relieve dyspnea

Treatment of Paralysis

The treatment of paralysis caused by poliomyelitis will not be discussed in this chapter at any great length The complex details involved in immobilization of paralyzed muscles different types of physiotherapy muscle training and surgery with its various corrective and stabilizing operations are too specialized to be properly discussed here Certain simple principles of treatment may be outlined although at the risk that over simplification may lead to inaccuracies Until the last few years at least most orthopedists agreed on the following general procedures

1 Immobilization of paralyzed muscles to be effected by suitable

first only in the anterior part of the mouth. Its most effective use is with a metal aspirator that can be placed in the throat exactly where it is needed. A rubber tube, although it seems soft and least likely to be traumatic, often cannot be directed effectively.

Atropine, in an effort to dry up secretion, does more harm than good. It may result in the production of thick, sticky secretions which are even more difficult to remove, and the effect of atropine itself on the rate of the heart in bulbar poliomyelitis is to be avoided.

The handling of the excitable and nervous patient needs further comment. Anxiety and fear of choking make the patients with pharyngeal paralysis much more difficult to treat. The more frightened they become the more the secretions bother them and the greater their fatigue becomes, so that aspiration of the throat can be carried out only with such a struggle as to nullify its value. A calm reassuring attitude, deliberate and firm action on the part of the doctor and nurse, the avoidance of a state of confusing bustle and hurry are of great importance.

In spite of the greatest skill by nurses and physicians in preventing aspiration and in keeping the pharynx free of secretions, success will not always follow. An acute attack of cyanosis due to choking on inhaled secretions or vomitus seems seriously to aggravate the underlying pathological condition due to poliomyelitis virus in the anterior horn cells. At least, after such an attack, patients are often dramatically and permanently worse. It sees quite probable that generalized anoxia has a direct effect on the course of the disease in the central nervous system. The use of tracheotomy to prevent such a situation is therefore clearly indicated. The problem is to carry out the tracheotomy before an acute attack of cyanosis makes it obvious to everyone that it is necessary. It requires good judgment and careful observation to determine this point. A tracheotomy is obviously a serious and mutilating operation and although in poliomyelitis, if the patient is in the acute stage of the disease, it should leave no serious results, nevertheless it is a step not to be undertaken lightly. Although in most cases of pharyngeal paralysis it can be avoided, a tracheotomy to produce a free airway and allow sleep is indicated in certain patients, particularly in the high strung nervous type. This procedure has been advocated recently with such enthusiasm that many seem to believe that a tracheotomy for all swallowing difficulties in poliomyelitis is to be advised. This obviously is quite wrong. The need for this operation usually can be determined by a few hours of critical observation. The emotional attitude of the patient, his response

to aspiration and postural drainage can give one a good idea of the need for tracheotomy before one gets into great difficulties

One should demand that a patient under the more conservative method of postural drainage and aspiration should be able to get such relief that he can relax and go to sleep If he cannot one can be sure that the condition will get progressively worse and that fatigue will greatly prejudice the chances of a successful outcome Sometimes it is extremely difficult to determine whether the irregular respirations are due to pharyngeal secretions or to damage to the respirator centers themselves in the brain stem A tracheotomy here does not seem logical However it is often difficult to make a clear distinction as to which is causing the symptoms we see and if uncertainty exists after careful observation a tracheotomy is justified even though the patient may die soon after Rarely adductor paralysis in the larynx may contribute to or cause respiratory difficulty and such a situation is clearly an indication for tracheotomy

The use of oxygen is entirely logical whenever there is an interference with pulmonary ventilation The use of oxygen by a closed tent should not be resorted to however in such a way that other and more direct attempts to relieve respiratory difficulty cannot be carried out or that constant observation is prevented Many patients have died by neglect in oxygen tents simply because they were not carefully observed there and the clinician relied too much upon the administration of oxygen as a panacea for respiratory difficulty It must also be clearly understood that oxygen administration may increase the oxygen in the alveolar air but cannot aid in the excretion of carbon dioxide in respiratory difficulty and therefore may not relieve dyspnea

Treatment of Paralysis

The treatment of paralysis caused by poliomyelitis will not be discussed in this chapter at any great length The complex details involved in immobilization of paralyzed muscles different types of physiotherapy muscle training and surgery with its various corrective and stabilizing operations are too specialized to be properly discussed here Certain simple principles of treatment may be outlined although at the risk that over simplification may lead to inaccuracies Until the last few years at least most orthopedists agreed on the following general procedures

1 Immobilization of paralyzed muscles to be effected by suitable

splints casts or other means of fixation for the period of muscle tenderness or spasm which may last several weeks or months

2 The application of heat during the acute stage to tender muscles by the use of hot packs This has been emphasized always as important for comfort if not for any specific effect on the course of the disease that might result

3 The cautious initiation of physiotherapy technics for the stimulation and re education of weakened muscles and prevention of contractures always carried out to a point short of fatigue, with immobilization being reapplied in the hours of the day not given over to such physiotherapy

4 During a final stage after most muscle function has returned that will return the use of muscle transplant and stabilization operations on the joints to permit the most efficient function of residual muscle power

Recently conceptions as to the nature of paralysis and its treatment have been advocated by Elizabeth Kenny of Australia and her disciples which are considerably different from what has been customarily accepted in the past Greater emphasis has been placed on the heat treatment of tender muscles during the acute stage not simply to relieve pain but as a procedure actually preventing paralysis Immobilization by casts and splints has been discarded Muscle re education with active participation by the patient is begun early in the disease as soon as muscle tenderness relieved by the hot packs allows it

Miss Kenny and her disciples have made broad claims for the efficacy of such treatment These claims have reached the public eye and her method of treatment has been widely carried out by many groups of physicians so that a short discussion here is justified They have taught that there is actually no true paralysis as it was ordinarily understood in poliomyelitis but that all paralysis which is apparent is due to inhibitions of muscle function or in their words "alienation" by tenderness or spasm in opponent muscles They teach that paralysis results only if tenderness and spasm is not reduced or eliminated by the use of hot packs applied in a very specific manner Their concept that the actual pathogenesis of the disease is not by destruction of anterior horn cells but by other neuropathic effects of the virus has been supported by an apparent rediscovery and new interpretation of the pathological findings of the acute disease that is the perivascular infiltration and the generalized interstitial injection in addition to changes in the anterior horn cells Although their explanation of the physiological disturbances in polio-

myelitis is stated here too simply to be accurate it hardly deserves more serious discussion

Following the concept that pain and spasm play a large part in causing paralysis the use of various other procedures in addition to hot packs to reduce spasm or its effect has been advocated One group of workers advocates the use of a curare like preparation to paralyze temporarily muscles in spasm this to allow the general use of muscles that apparently were first paralyzed This combined with stretching or overstretching of muscles in spasm has been carried out by certain physicians with enthusiasm

It is hard to evaluate accurately these various claims at this time Studies with electromyograms as well as accurate clinical observations indicate that there is no dependable relationship between muscle tenderness and spasm and paralysis It does not require much knowledge of anatomy to make one skeptical of the existence of muscle groups in spasm that could act as opponents to the contraction of the pharyngeal muscles *or the diaphragm Unfortunately as has been true with other adventures* in the therapy of poliomyelitis attempts at treatment have been carried out without proper control studies without proper muscle examination and apparently with a great lack of experience and knowledge as to what happens in the natural course of the disease Since even with meticulously careful muscle examinations a good deal more than a quarter of all patients with spinal fluid changes have no detectable paralysis and at least a half have only trivial paralysis it can be seen how easy it is to give credit to any form of therapy that is generally applied during the acute stage of the disease Much of the apparent paralysis is transitory and moreover when pain or spasm exists it is extremely difficult to make an accurate muscle examination It has long been noted that improvement in muscle function takes place over periods of months and years It is hard to determine how much of this has taken place by nature *alone and* how much has been effected by treatment of some sort that has always been carried out but a certain amount of improvement always takes place no matter what the treatment Sudden, almost dramatic improvement has occurred and has been reported at various stages sometimes *after periods of months* both with no treatment and after some particularly well advocated treatment Obviously no form of therapy in this disease can be accepted as effective unless one critically *evaluates it in* the light of the spontaneous variations which may take place

Experience has answered already some of the questions about the Kenny treatment Certainly it can be said that the vast *majority of*

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physicians do not believe now that the treatment prevents paralysis although they may believe that it diminishes it The rigid therapeutic program outlined originally is gradually being carried out with less fetish like enthusiasm and attention to detail However a great deal of good can be attributed to this latest therapeutic venture in that it has called attention in a critical way to technics in the treatment of poliomyelitis honored only by time, and it has stimulated a great deal of research and new thought which cannot but result in progress Undoubtedly immobilization of tender or paralyzed muscles was carried out far too intensely and too long in the past and much atrophy of disuse resulted

An attempt to outline briefly what is considered at present by a good many physicians to be good treatment might be made In the first place the relief of pain in the acute stage by the use of hot packs applied sensibly in moderation over a limited number of days or weeks and on the basis of definite subjective relief is generally accepted There has been a great reduction in the use of immobilization technics and opportunity is given the patient to move around in bed and to use partially paralyzed muscles to the limit of his desire short of fatigue and pain Gradual attempts at passive motion and muscle re education is accepted as of very great importance The technic of muscle re education requires specially skilled technical workers with a good knowledge of functional anatomy and a personality that can induce a timid patient to conscious endeavor to use each muscle Undoubtedly great improvements in function take place as a result of skillful muscle re education not only in poliomyelitis but in many other conditions whether or not associated with pain Finally the use of supporting braces splints or stabilizing operations to allow the patient to make whatever use he can of what muscles he has left is of great importance

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CHAPTER VI

DIPHTHERIA

By EDWIN HEMPHILL PLACE

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Definition — Diphtheria is an acute contagious disease consisting of a local infection usually of the mucous membrane of the upper respiratory tract, less frequently of the skin wounds and some other mucous membranes, characterized by a local inflammation with a fibrinous false membrane and by a toxemia producing among other changes, degeneration of peripheral nerves and of muscles especially of the heart

History

Aretaeus of Cappadocia 2nd-3rd century A D described diphtheria as ulcera Syriaca and Aetius 6th century A D gives a description of epidemic diphtheria not unlike Aretaeus He first described palatal paralysis in the disease From 1581 to 1630 many epidemics occurred in Spain and Italy and rather complete accounts are given by Jeronimo Gil Pina (1636) and by Pedro Miguel d Heredia (1665) John Fothergill in England wrote of diphtheria in 1748

Samuel Bard of New York in 1770 described an epidemic of diphtheria as angina suffocativa Bretonneau 1826 wrote an excellent monograph and gave the name of diphtherite He did one of the earliest successful tracheotomies in 18 5

His pupil Trousseau became a distinguished authority on tracheotomy and devised the tube now in use He gave the present name diphtheria Bouchut also in Paris devised an intubation tube for laryngeal diphtheria in 1856-58 but it was unsuccessful and was strongly opposed by Trousseau Joseph O Dwyer of New York independently of Bouchut devised an intubation tube in 1880-85 by extensive trial and error which is essentially the same as that now in use He was greatly aided by a young German workman George Ermold O Dwyer s intubation replaced tracheotomy in the Trousseau wards

Klebs 1883 first described the diphtheria bacillus and Loeffler first cultivated it in 1884 Roux and Yersin demonstrated the diphtheria toxin in 1888 and von Behring discovered antitoxin in 1890-1893

Bela Schick devised the test for susceptibility in 1913 and in the same year von Behring reported active immunization with toxin antitoxin Ramon of Paris produced anatoxin in 1924 and demonstrated the superiority of this non toxic agent for immunization Glenny precipitated the toxoid with alum in 1930 this has contributed so much to modern immunization

Etiology

Diphtheria is caused by the *Cornebacterium diphtheriae* discovered by Klebs in 1883 and more fully studied and isolated in pure culture by Loeffler in 1884 The bacillus is found on the surface of the mucous membranes and the pseudomembrane of the infected areas It is always present in the inflammatory areas of diphtheria

during the acute disease but tends to disappear rapidly after the subsidence of the inflammation It may persist for days weeks or months however and at times even years particularly if there is some abnormality to provide a favorable nidus

Diphtheria bacilli may be found on the mucous membranes of healthy persons who give no evidence of ever having been ill and who are shown to be immune by the Schick test They also may be present in various mucous membrane inflammations in persons who are immune to diphtheria as shown by the Schick test the clinical course and therapeutic test These are exceptions however and do not invalidate their causal relationship with diphtheria Loeffler and others have produced with the organism lesions in animals simulating in every way the clinical manifestations of diphtheria The organism is found invariably in cases of typical clinical diphtheria Toxin obtained from pure cultures of *C diphtheriae* produces in animals the characteristic paralysis of diphtheria and by continued local application the typical local inflammation with characteristic membrane

The morphology and cultural characteristics of the *C diphtheriae* are described in the various books on bacteriology to which the reader is referred Roux and Yersin established the presence of a soluble toxin in 1888 and 1889 In guinea pigs very small doses of the toxic bouillon filtrate 0 002 c c may cause death

Certain clinical and laboratory facts regarding diphtheria toxin are essential to a clear understanding of the disease and its treatment (1) The toxin is absorbed rapidly by the tissues and reaches the blood stream ( ) It is not secreted in appreciable amounts into the cavity of the throat and cannot be washed out by gargles (3) The quantity of toxin produced in a case cannot be measured but the severity of the local inflammation and the degree of toxic after-effects are crude measures the amount of antitoxin necessary to save the patient is of value but the need of a margin of safety prevents this being accurate (4) The toxin probably combines with many body tissues but only in a few as the nerves the heart and other organs are harmful clinical effects found For example in the Schick test the toxin combines largely if not solely with the cutaneous tissues while clinical evidence of effects of diphtheria on the true skin is practically nil except where there is local infection Differences in the affinity of the various tissues for the toxin may account for striking variation in the after effects in cases of apparently equal severity as shown by the local process (5) The absorbed toxin acts with great rapidity on the tissues so that an effect which will prove fatal may be produced in thirty six hours or even less the toxin in the Schick test is practically all fixed by the tissue within twenty hours (6) It has not been shown that toxin tissue combinations may be broken by antitoxin or other treatment but when antitoxin is present in the blood stream the toxin always combines with it rather than the tissues (7) In susceptible animals

toxin leaves the blood stream with great rapidity, while in non susceptible animals as turtles it may remain in the blood for long periods

Diphtheria bacilli may be virulent or avirulent the latter produce no disease in man so far as known and probably do not become virulent later Determination of different types by Hammerschmidt in 1924 and later by Anderson and associates in 1931 at Leeds has enormously stimulated interest, but final conclusions still are pending

The main differences as determined by Anderson and his colleages were as follows

Type	Tellurit Colony	Hemolysis	Broth	Starch Fermentation
Gravis	dark rough	o	granular	+
Mitis	black smooth	+	even turbidity	o
Intermediate	intermediate	o	fine granular	o

The gravis type as its name indicates was found in malignant cases with marked swelling and bull neck and often little membrane and did not respond well to antitoxin An increase in mortality of diphtheria which had been occurring in Germany and in other continental areas and in Britain was believed to be related to this severe form

Epidemics due to the gravis type in this country occurred as in the Halifax epidemic and in Belair Md The mortality was under 5 per cent, which is not worse than our customary mortality and the epidemic was controlled following immunization and the usual therapeutic procedures Studies by Frobisher and many others would throw doubt on malignant forms being due to any one type of *C diphtheriae*

Diphtheroids belonging to the cornebacterium family, differing from the *C diphtheriae* in cultural tintorial and especially, in lacking toxigenicity are common and widespread and have no known connection with the disease It has been shown recently that strains non virulent for guinea pigs and rabbits are virulent for mice on intracerebral injections Frobisher has shown also that the avirulent form may immunize rabbits against virulent bacilli but not through stimulation of antitoxin production

IMMUNITY

Natural antitoxic immunity is very frequent Over 50 per cent of the population are immune Roemer and others have shown the frequent presence of antitoxin in normal individuals and found that $\frac{1}{30}$ unit per cubic centimeter of the blood serum was sufficient to produce immunity A simple and practical method of detecting immunes was developed by Schick

Fraser by means of diphtheria antitoxin titres of blood has shown that 0 01–0 004 units per c c may more nearly represent the immunity level

Schick Test — One fiftieth of a minimal lethal dose of diphtheria toxin is injected intracutaneously usually in the flexor surface of the forearm No reaction occurs if the patient is immune as the toxin is neutralized If he has less than $\frac{1}{250}$ unit per c c of blood however local redness and edema occur within 24 to 48 hours rarely later This is usually 1 to 2 centimeters in diameter but may have an areola 3 to 5 centimeters in diameter The reaction increases for 3 to 4 days and usually subsides in 7 to 10 days leaving a certain amount of pigmentation for weeks or at times months The skin over the deep red area usually becomes wrinkled and hard and desquamates as the reaction subsides

TABLE I

Age Distribution of Schick Positive
In New York (Zingher 1923)

Schick	Per Cent Positive	Schick	Per Cent Positive
0–6 months	56 6	10–20 years	14 2
7–8	63 4	20–30	11 6
8–9	83 8	30–40	10
9–10	93 1	40–50	8 2
10–11	87	60–70	5 4
11–12	91 1	over 70 years	5 5
1–3 years	83 2		
4–6	58 6		
7–10	36 5		

Tufts Medical Dental Students
(Wheeler 1943–1946)

Schick	Per Cent Positive
18 19 years	25
20–21	38
22	48
23–24	47
25+	4 4

These figures include persons (± 50 per cent) who have had booster doses of toxoid 2 to 3 days before testing

False reactions occur frequently in older children and adults and less frequently in younger children These are protein reactions due to the bacterial substance from organisms that have broken up or to substances in the media They are not inhibited by antitoxin as is the true Schick reaction A control test should therefore be done The toxin is heated to 75 C for one half hour and then injected as in the previous tests False reactions appear as a rule within 24 hours often in a few minutes and tend to subside in 48 to 72 hours They are more diffused and poorly defined and less likely to produce local pigmentation and desquamation In reading the reaction it is desirable to examine at 48-hour 4-day and 7-day intervals

When both are negative the patient is immune When the Schick is positive and the control negative, he has no antitoxic immunity The age distribution of Schick positive persons is shown in Table I If both show a reaction it is more difficult to determine immunity but it may be done by the difference in course if positive and if negative often by the short duration of both reactions *i e* 24 to 48 hours

Care must be used in the test, which is an accurate quantitative one that the toxin dose is accurate that it is all injected and that the reading is carefully done

Old toxin is used which has become fairly stable so that under conditions of cold and dark no practical loss of toxicity will occur in 3 to 4 months Dilutions are made as needed so that 0 1 c c equals $\frac{1}{50}$ minimal lethal dose Stabilization of the diluted toxin is now secured by human albumen The injections are made with a glass Luer type syringe, and there must be no leaking around plunger or needle hub The injection must be intracutaneous so that a well marked wheal usually about 0 7 centimeters occurs

It is obvious that immunity is relative and although large experience has shown the relative safety of Schick negative persons from diphtheria recent studies throw grave doubts on the amount of antitoxin needed to protect Ipsen in studies of blood antitoxin titres early in diphtheria found in some fatal cases as high as 100 units per c c It was unknown what the antitoxin level was before infection but it is unlikely that it could rise so high during a few days after onset The significance of these cases will have to await more study None of the previously immunized cases in his series died

Acquired immunity from attacks of diphtheria varies greatly It may last for years or may be lost in a few weeks This probably varies with the amount of antitoxin production by the body as homologous antitoxin remains much longer than that from the horse Second attacks however are not rare and have occurred within 2 weeks although usually at longer intervals

Artificial immunity will be dealt with later in the article (see Prophylaxis)

Immunity other than antitoxic undoubtedly occurs but is more difficult of demonstration In the inoculation of animals scarification of the mucous membrane usually is necessary After operations on the throat and following diseases injuring the mucous membrane such as measles and scarlet fever diphtheria is more likely to occur than in healthy persons On the skin also diphtheria only occurs when there has been preceding injury This barrier immunity is undoubtedly of considerable protection both in diphtheria and in infections in general

Incidence

Incidence of diphtheria corresponds in a general way with the susceptibility

as shown by the Schick test (see Table I) The highest incidence is reached at 3 to 5 years of age, although the highest susceptibility is at 1 to 2 as shown by the Schick test Besides difference due to chance this may be due to greater contact with others as the child grows older Diphtheria occurs widely over the world but prevails more, and in more serious form especially in temperate zones Since active immunization has been done largely in children and the natural immunization from contact has decreased adults are now becoming victims more frequently

Contagiousness

Contagiousness is much less than in measles where droplets and a very high natural susceptibility are important features or in smallpox where the contagiousness is striking The penetrability or power of invasion of the organism is apparently much less than in the above Certainly antitoxically susceptible persons often escape although brought in contact with diphtheria Fairly intimate contact however is necessary to transmit the organisms from one person to vulnerable points of another

The nasal form of the disease is by far the most contagious as the discharge through methods and habits of handling may be spread readily about by contact handkerchiefs towels lavatories candy toys hands garments etc Moreover nasal cases very often escape early detection under the guise of colds and allow a longer period of contact than other forms This type also tends to mild constitutional and local signs and to a slow and prolonged course Most extensive contact epidemics in home school or asylum may be traced to this form

The laryngeal cases on the other hand are the least contagious and in the early days this absence of contagiousness was held in part as showing its different character from faucial diphtheria

Duration of contagiousness varies greatly In some instances it is as short as a few days while in others it may be months Epidemiological evidence rarely shows contagiousness of months duration but bacteriological studies have shown occasional carriers of years duration In more than half the cases the organisms disappear within a few days after the subsidence of the inflammation

Manner of Spread — Diphtheria is spread by direct contact by indirect contact by droplets and by infected milk Probably nearly 90 per cent of the cases are acquired by direct contact with patients ill with the disease

Mild and missed cases and carriers are of great importance in the spread of disease and carelessness in personal hygiene which allows the easy transfer of secretions of the nose and throat makes such cases always dangerous Chapin has thrown great and proper emphasis upon this point

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TABLE II

LOCATION OF DIPHTHERITIC PROCESS IN 1470 CONSECUTIVE CASES 1926–1932

	Number	Per Cent Cases	Per Cent Mortality
Faucial	770	52.38	3.03
Faucial and Laryngeal	195	13.26	12.81
Nasal	163	11.22	1.21
Faucial and Nasal	155	10.54	23.22
Laryngeal	129	8.76	6.07
Faucial Nasal and Laryngeal	41	2.78	31.0
Laryngeal and Nasal	12	0.81	33.00
Eye	2		0
Skin	1		0

Total cases for each localization

	Number	Per Cent
Faucial	1 156	80
Laryngeal	377	2 6
Nasal	18	14.8

Note — Pulmonary localization is omitted from these figures although frequently present in the laryngeal cases

Faucial Diphtheria

In this form the most characteristic appearances occur The tonsils and lymphoid structures are the most frequent point of attack but the adjacent pillars uvula and soft palate are involved frequently The onset usually is insidious but may be abrupt The severity of onset does not necessarily indicate the course as a mild insidious onset may lead into the most severe types and sudden onset may be followed by a mild favorable course

There are no characteristic symptoms at onset Malaise lassitude or listlessness is common, sore throat alone or with focal signs due to other involvements such as nose larynx etc almost always is present fever usually is slight vomiting and headache may occur Usually the general toxic symptoms are slight and may be practically absent even in cases which prove very severe or fatal but in some cases they may be severe with prostration twitching mild delirium high fever or even convulsions

Fever usually is from 100 to 103° F rarely over 104° It may be absent It is certain that often the fever at onset rapidly subsides although the local process may continue so that many severe cases have a normal or nearly normal temperature when the physician is first called The fever curve is no guide to severity or course of the disease

Prostration usually is slight certainly at the beginning In severe cases it may become very marked toward the third or fourth day Lassitude is very

INCUBATION

The incubation usually is short, 1 to 3 days In some cases however the organisms are harbored for days and weeks without symptoms and then finally produce the disease Knowledge of the incubation period is of no practical clinical value as the organisms can be detected by cultures made from the patient's throat and immunity may be secured by antitoxin or toxoid injections

PATHOLOGY

The pathological lesions of diphtheria are of two kinds local and general All lesions are due to the action of the specific toxin although lesions due to the invasion of the tissues by secondary invaders especially the streptococcus occur The local lesions are characterized especially by the presence on the surface of the mucous membranes of a fibrinous false membrane For a description of the local and general pathological changes found in diphtheria the reader is referred to any good textbook on pathology

It is difficult to define the part played by secondary invaders in contrast to that played by the diphtheria toxin in the production of lesions in the disease Undoubtedly many of the lesions are solely or chiefly due to the diphtheria toxin as are the nerve degeneration and probably the characteristic local lesions Other lesions may be due to combinations of these secondarily invading organisms with the diphtheria toxin as in the lungs, nasal sinuses etc, while others are due purely to the secondary invasion as abscesses etc A great variety of focal or general infections may occur

CLINICAL PICTURE

Diphtheria is a local infection with varying degrees of inflammation characterized by dull redness, usually slight to moderate in intensity by swelling slight to marked and by false membrane deposit From the local infection toxin is absorbed which causes a general toxemia with varying but often mild toxic symptoms and resulting often in nerve degeneration with paralysis and cardiac neuromuscular degeneration

The clinical appearance varies extremely with the severity of the disease and also with the area affected and will be described for convenience under the headings of faucial diphtheria nasal diphtheria laryngeal diphtheria and a few other types (see Table II) All sorts of combinations of these types occur although the disease may be limited to any one of these areas The infection may start at one area and progress or jump to other areas as the disease progresses

it often develops with extraordinary rapidity and covers the swollen area in a few hours and in a day or two may become very thick and firm The uvula may be swollen and fill the space between the tonsils or be crowded up by the tonsillar swelling behind them or in front at the base of the tongue

Swelling of the neck usually occurs in these severe case first at the angle of the jaw, often extending as the proce s increases completely around beneath the chin and down on the chest as far as the third rib This consists of the same type as in the throat and is soft elastic and only slightly tender as a rule and is not brawny or red as in streptococcus cellulitis If the throat infection is limited to one side the swelling corresponds The lymph nodes usually are swollen also but may not stand out in the general edema of the surrounding tissues This swelling is due to the toxin extending through the lymphatics and does not break down but subsides with great rapidity when antitoxin has neutralized the toxin Exactly similar swelling is seen in subcutaneous toxin injection in guinea pigs Bacterial invasion may occur also most frequently with the streptococcus but it is chiefly limited to the lymph nodes and organisms do not invade the tissue as in scarlet fever Abscess therefore usually is limited and late and the phlegmonous cellulitis of Ludwig is not seen

Membrane u ually appears early in the inflammation but may not be present until 3 or 4 days after the inflammation begins In color it is usually grayish white or translucent white but may be yellowish brownish or black in areas due to food drugs hemorrhage into or below it and to saprophytes It turns to white as it clears In consistency it is firm elastic and tends to keep its form even if removed from the surface When thin it may be friable and as it begins to soften and dissolve or to be thrown off it tends to be friable especially if not very thick In this respect it acts as fibrin does under artificial digestion

The membrane usually is well anchored to the tissues and is not easily de tached until it begins to be softened by the lytic substances in clearing If it is removed while the inflammatory process is continuing slight hemorrhagic spots are seen on its undersurface and the subjacent tissue also tends to slight hemorrhage The denuded area rapidly often in a few hours becomes covered by another membrane In the trachea but less so in the larynx the membrane may be more rapidly separated from the mucous membrane on account of the firm basement membrane and the thinner epithelial layer so as to be coughed up or to act as a foreign body in the larynx

The contour of the membrane usually is rounded and not irregular or dentate and the edge is raised and sharply defined The membrane tends to occur evenly over the involved area and therefore to occur in single or few patches rather than to be multiple It may however take a follicular form It may be heaped up in crests like blown snow While frequently symmetrical it may occur in any part of the throat alone Depending on severity and duration of the disease

common and may be the only symptom Restlessness in sleep, sleepiness or dullness are frequent but the child is readily roused unless the disease is advanced when the stupor may become very marked Delirium usually is absent and when present is not very active and may be noted only when the child is dozing Convulsions are infrequent and are present practically only in infancy In the mild cases nervous symptoms are infrequent

Nausea and vomiting occur in the more severe cases and have been present in about 25 per cent of my cases In cases with gastric involvement vomiting may be severe and constant Constipation usually is present diarrhea very rarely Appetite is variable but usually not good Abdominal pain or distress is occasionally the first symptom

Sore throat usually is complained of but this is by no means certain and even in severe cases and in older children may be absent although the throat is filled with membrane Dysphagia is marked when the pharyngeal wall is affected but slight in most cases otherwise Rawness and soreness on swallowing and not severe pain as in peritonsillitis are the rule The local inflammation usually is distinct by the time symptoms draw attention to the patient and marked and extensive involvement may be found on routine examination at times when the child was not known to be ill The inflammatory reaction may be localized or extensive unilateral or bilateral, asymmetrical or symmetrical and vary from a slight redness the so-called catarrhal type to a very extensive swelling with membranous deposit which fills the throat

In the occasional cases seen before the membrane forms the redness is best seen It is dull pinkish to deep red and may have a slightly cyanotic tinge When much edema of the tissues is present it has an appearance not very different from a polyp Mild cases show redness as the only sign and can be recognized with certainty only by cultures and confirmed by the Schick test When membrane is present the redness typically appears at its margin as a narrow zone $\frac{1}{8}$ to $\frac{1}{4}$ inch wide In rapidly advancing cases the redness is more diffused and in slowly developing cases there may be no appreciable red zone around the membrane The character and extent of the redness is one of the important differential signs

Swelling indicates a severe type In mild or moderate cases it may be hardly noticeable or limited to swelling of the tonsils In severe cases the swelling may be very great involving the tonsils pillars and uvula so as to occlude the throat and cause dyspnea and dysphagia which may necessitate tracheotomy Edema may be unilateral or bilateral and usually is soft and elastic in consistency and causes less pain and less difficulty in opening the mouth than similar swelling in peritonsillitis In such cases the swelling may precede the formation of membrane by from 1 to 3 days and sometimes longer and to the uninitiated may not suggest diphtheria When membrane forms in these phlegmonous cases

ginning As the disease advances it is likely to be lower and in the early convalescence usually the second week is at its lowest about 70 to 100 In the presence of the cardiac involvement it may drop to unreadable points

The pulse usually is moderately elevated ranging from 100 to 120 in moderate cases In severe cases it may be very rapid and this indicates severe toxemia In laryngeal cases because of dyspnea and excessive work the pulse rate is especially rapid

Ulceration is not characteristic of diphtheria and previous to subsidence is never seen in uncomplicated cases The so-called necrotic membrane of the severe cases clears with striking completeness and rapidity as convalescence occurs In the severe and more extensive cases shallow ulcerations are seen on tonsils pillars uvula or soft palate as the membrane comes off These heal rapidly in the course of 7 to 10 days without evident scarring Perforation of the palate deep sloughs and hemorrhage from large vessels have not been seen in my wards except in clearly streptococcic infections

There still remains doubt of the cause of malignant forms of diphtheria many workers considering that streptococci play an important part The local reaction in these cases however usually is distinguishable in its type and course and response to antitoxin from streptococcic infection So that if significant at all the streptococcus increases the reaction to or the virulence of the diphtheria bacillus

Blood — A moderate leukocytosis of from 10 000 to 30 000 of the polymorphonuclear type usually occurs Complicating infection as broncho-pneumonia otitis media etc may increase the count while measles may reduce it strikingly The count usually is highest at the height of the disease and drops with convalescence In fatal cases it may remain high or at times drop as the disease progresses Loss of red cells was marked before the use of antitoxin according to Billings from the fifth to the fifteenth day the drop varying from 470 000 to 2 040 000 per cubic millimeter averaging a loss of 510 000 There is a corresponding loss in hemoglobin Since the use of antitoxin these changes are slight and the severe anemias of convalescence that were formerly reported are rare

Urine — During the acute stage albuminuria is common but its frequency has been much less in the cases under my observation than has been reported frequently especially before antitoxin While autopsy evidence suggests marked kidney injury clinically the damage usually is slight I find no diagnostic aid in the urine

Course of Faucial Diphtheria — The height of the disease if untreated is usually reached in from 2 to 8 days although rarely as late as 12 to 14 days Up to this time the toxemia increases often rapidly and the local inflammation augments both in intensity and extent The general toxic symptoms may in

and the location of the organisms it may be thin or thick, small in area or occur over the whole throat, cover tonsils, pillars, uvula, soft palate and pharyngeal wall It occurs rarely on the buccal mucous membrane, tongue or lips most such cases however are not diphtheria

The clinical appearance of the diphtheria patient with faucial involvement thus is seen to vary tremendously On the one hand is found the relatively slightly ill patient with a small, limited diphtherial inflammation of the throat and on the other a somnolent toxic prostrated patient with great swelling and extensive membrane of the fauces swelling of the whole neck and upper sternal regions with dysphagia and dyspnea and often with nasal involvement showing nasal discharge obstruction and often hemorrhage Other involvements and complications may modify the picture still further varying with the severity of the attack

Hemorrhage may occur especially in the severe case with constant oozing into the throat and sometimes with severe hemorrhage Especially in nasal cases does hemorrhage occur at times sufficient to blanch the patient and even to lead to or hasten death Hemorrhage from the organs as the kidneys may occur Hemorrhages into the skin, especially of the thorax and also into the mucous membranes of the mouth occur in severe cases and are of grave prognostic import Hemorrhages in such cases frequently are found post mortem in the pericardium and pleura and may involve a large area

Thrombocytopenia may occur producing symptomatic purpura but usually the hemorrhages are not related to deficiency in clotting

Diphtheria is not characterized by any eruptions and the presence of any eruption except the purpuric throws doubt on the diagnosis In rare cases of typical diphtheria however eruptions may occur These may be due to toxic effects on the vasomotor system to drugs and to local causes In general they are irregular multiform transient and more likely to occur on the extremities Differentiation always should be made carefully from the exanthemata especially scarlet fever and measles but it must not be forgotten that a scarlatiniform rash would throw a very great burden of proof on the diphtheria diagnosis Rashes resulting from serum treatment will be considered under that heading

In severe cases especially a rather characteristic odor of the breath is found This is a peculiar sweet close putrid odor and may make the room so offensive as to disturb others Many feel that this odor is sufficiently characteristic for diagnosis Many cases especially the mild or early ones however present no odor and the diphtheria bacillus certainly is not itself responsible Similar odors are found in septic throats and in Vincent s angina The odor probably is due to saprophytic organisms in the membrane and certainly the character of the inflammatory reaction is a more reliable diagnostic evidence than the odor

The systolic blood pressure usually is low but only moderately so at the be

discharge is sponged away or is blown out the typical diphtheria membrane may be seen on the septum or turbinates or even lining the whole cavity Edema of the neck and lymph node infection do not occur In the milder cases the discharge may be so slight as to show only in yellowish or brownish crusting which recurs on removal Picking the nose may lead to septal ulcers

Course of Anterior Nasal Diphtheria —The course usually is prolonged for days to weeks if untreated by antitoxin so that this may be classed in the subacute or chronic forms unlike the faucial involvements It usually does not advance and because of its mildness often is unrecognized for long periods When antitoxin has been given or has been produced by the patient the nasal discharge rapidly subsides and the obstruction or crusting disappears Appearance of the infection in the throat or larynx may rapidly change this picture

Nasopharyngeal Vault Diphtheria

Diphtheria of the nasopharyngeal vault if primary often is very obscure It is often of severe type and toxic absorption is rapid and severe Toxic constitution symptoms may be rather more marked than in the faucial type so that fever lassitude prostration and restlessness may be fairly marked even early Nasal obstruction and nasal discharge may be marked but in some cases may be absent In many cases during the first two days little may be found on physical examination to account for the illness unless the nasal vault is inspected Swelling of the neck at the angle of the jaw is frequent and often early and may become extensive as in faucial diphtheria

The inflammation may spread downward into the throat and the membrane spread over soft palate pillars and tonsils or the pharyngeal wall or anteriorly into the nose In some cases the palate becomes swollen and membrane is found covering the posterior aspect or the membrane may appear along the borders or be deposited anteriorly Discharge usually is fairly marked dropping in the throat or running from the nose The voice may be thick or nasal

In combination with faucial involvement this type is the most dangerous toxically and fatalities and later toxic effects as cardiac and nerve degeneration are striking

Laryngeal Diphtheria

The laryngeal type of the disease is the most serious because of respiratory obstruction and bronchopneumonia Toxic absorption is slight and in primary laryngeal cases diphtheritic cardiac degenerations and paralysis do not occur This is probably due to the physiologically unfavorable conditions for absorption

crease slowly and restlessness anorexia stupor and prostration develop In many cases however the toxic symptoms at the onset subside the patient feels better is active and cheerful and the parents are misled into thinking that the patient is recovering from his indisposition In 3 to 4 days, with the advance of the disease however prostration begins great lassitude and stupor develop and with swelling of the neck and throat odor to the breath hemorrhages into the skin or from the mucous membranes the appearance becomes alarming Difficult breathing may occur from the throat swelling or extension to the larynx The blood pressure becomes low the pulse weak the hands and feet cold and the patient sinks into lasting sleep If dyspnea is absent the suffering usually is not marked and death comes finally so easily as often to deceive the watching parents

Consciousness usually is retained till the last and often if roused from his stupor the patient will say that he is all right If on the other hand the course is favorable with development of sufficient antitoxin the disease progress ceases the redness and swelling subside the membrane whitens begins to soften break up or dissolve or is loosened from the mucous membranes and thrown off the fever if present subsides the odor disappears and in a few days to a week or ten days the patient is apparently normal

The subsidence of the symptoms and the local process however, does not indicate that the patient has successfully combatted the enemy as insidious damage to the heart and nerves may have occurred which will cause serious effects or death during the convalescence Secondary infection with the streptococcus staphylococcus pneumococcus and other organisms may occur either during the acute course or after subsidence of diphtheria to modify this course These will be treated under the complications

Anterior Nasal Diphtheria

Diphtheria of the anterior nares is very common either alone or with faucial or other involvements and because of its mild and long course and great contagiousness is frequently the source of contact epidemics in schools asylums or homes The onset is mild and insidious and the constitutional symptoms mild or absent It is often thought to be a cold The fever is slight or absent malaise headache prostration and other subjective evidence usually are absent In the more active cases the discharge is profuse seromucoid but not frankly purulent There is often slight hemorrhage or blood streaks in the discharge and severe epistaxis may occur Epistaxis may be the first evidence of the disease but usually occurs later in the course Redness and excoriation of the nostril or the lip where the discharge comes in contact is common The infection may be unilateral but is more commonly on both sides Usually if the

When the stenosis becomes so marked that these efforts fail to supply sufficient air cyanosis appears and may become very marked especially in strong healthy children with rapidly developing stenosis The cyanotic stage is succeeded by pallor as exhaustion appears the struggling effort grows less and the heart fails The lips take on an ashen hue and the extremities may become cold The merging of the cyanotic stage into the pallid asphyxia accompanied by the decrease in respiratory effort and in struggling and the tendency toward stupor often has been misconstrued by anxious watchers as beginning improvement At the end unconsciousness becomes complete and death rapidly supervenes

It is seen that the chief signs of diphtheria of the larynx are not suggestive so much of toxic or inflammatory conditions as of mechanical interference with its dual function that of passage for air and phonation If examination of the larynx is made with the laryngoscope an appearance varying with the stage and degree of infection is found In general the local inflammation is like that of diphtheria of the throat but the characteristics are made out less readily because of the location Redness alone may be found rarely and is of a pale or deep color swelling of the mucosa may be slight or marked The aryepiglottic folds may be edematous *Membrane may cover the undersurface of the epiglottis* and line the larynx and trachea or it may occur as a small patch or patches The inflammation may be below the cords the membrane glistening on each side like another set of cords The membrane usually is firmly attached to the larynx but may be picked off with forceps and usually shows a bleeding surface Below the larynx the membrane is more easily removed from the tissue

Course of Laryngeal Diphtheria — As suggested in the account of clinical symptoms the disease if untreated tends to progress with more and more obstruction and more and more marked signs of oxygen deficiency This may be very rapid so that a high degree of obstruction is present in 24 hours or usually more slowly so that great dyspnea is present only after a few days The progress usually is fairly steady the signs gradually increasing but it may be modified at times by spasm attending the infection or by loosened membrane flapping in or out As a rule marked changes in the signs may be produced by varying activity of the patient so that in the early stage the child may show no evidence of stenosis when resting quietly but will show marked stenosis when crying or struggling increases the rapidity with which air must be supplied to the lungs

When well marked stenosis is present the distressing and striking picture will not be forgotten by one who has seen it The patient is anxious and restless and tosses about the bed or sits up trying in vain to gain a position which will secure the needed relief The respiratory muscles of the chest and abdomen are thrown into marked use with each respiration the chest yields to the great muscle pull and increased intrathoracic negative pressure showing retractions of the soft parts and bending of ribs and sternum The child refuses all ministrations

from the larynx and slightly to the fact that obstruction rapidly calls attention to the disease and leads either to treatment or to death from asphyxiation

The larynx is particularly liable to attack in infants and younger children The younger the child the more probable this form and the more fatal the outcome is The reason for this increased susceptibility of the larynx in early life is uncertain The slight development of the tonsils and lymphoid tissues the chief point of attack in older children may be somewhat responsible In cases whose tonsils have been removed diphtheria more commonly occurs in the pharyngeal wall than on the fauces It is possible also that the increase in incidence of larynx infection is due simply to decrease of the faucial form so that the increase is relative only Colds measles or other infections of the larynx certainly predispose to the localization of diphtheria here

The clinical evidence is very different in the purely laryngeal type from that of the preceding forms A croupy cough usually is the first symptom This ordinarily is fairly marked and becomes more and more pronounced often with rapidity In some cases however that finally prove very extensive the croupy cough is slight and infrequent It may be hoarse and barking or very high pitched metallic or reedy Toxic symptoms usually are slight or absent Fever ranges from normal to 102° F but very frequently is low and not rarely absent

Aphonia usually occurs in hours to days in some degree, slight to complete Aphonia may be absent however if the infection is localized below the cords or otherwise so as not to interfere with their closure Stridor is the most reliable sign of laryngeal stenosis It may appear very early or only after the infection has progressed for days but usually it is well marked in 3 to 4 days or less It is about equally inspiratory and expiratory and, though difficult to describe differs to the experienced ear in its timbre from the stridor in obstruction above the larynx or that below The pitch of the sound varies with the degree of stenosis and the force of the respiratory efforts with which the air is forced through the narrow larynx and may be high or low and vibrant With flapping membrane or loosened tubular casts either inspiratory or expiratory stridor may predominate Stridor is the only certain indication that dyspnea is due to mechanical obstruction

As the inflammatory obstruction increases dyspnea appears This may be very rapid so that nearly complete obstruction occurs in 24 hours although usually it is longer and in some cases not for several days The first sign of dyspnea usually is the use of the accessory muscles of respiration and stridor With the increase in muscle effort retraction at the suprasternal notch the ensiform and in intercostal spaces occurs In patients with flexible chests as in infants and young children bending of the ribs and sternum may occur, with flaring out of the lower ribs and funnel or pigeon breast sometimes to an extraordinary degree

In one of my cases a physician with tracheal involvement the whole right lung showed practically no respiratory murmur and when the patient turned on the left side severe dyspnea and coughing would appear due to the membrane dropping across the left bronchus as well Recovery was rapid and complete The onset had been a week earlier with cough lassitude and hoarseness and had led to the suspicion of tuberculosis The sudden attack of severe coughing was attended by expectoration of membrane

Whether diphtheria itself causes pneumonia in the pulmonary cases it is difficult to be sure Certainly diphtheria infection occurs low in the respiratory passages and bronchopneumonia merge with the laryngeal and tracheal picture Other organisms are invariably present however and many of the bronchopneumonias occur as the diphtheritic process is clearing and the patient is immune At times the pneumonia rapidly clears with the faucial diphtheria and points strongly to the possibility of a diphtheritic proces The large amount of antitoxin required in such ca es to secure clearing of a relatively mild throat infection also is suggestive

Ocular Diphtheria

Infection of the conjunctival sac occurs infrequently probably because of the protective mechanism and the less frequency with which infection may be carried to the eye as compared to the nose and throat When infection does occur it is of great importance because of the rapidity with which it may lead to blindness Rapid swelling of the conjunctiva occurs with puffing of the lids and a thin seromucoid discharge The membrane appears at first as a thin gray layer but may rapidly increase and become fairly thick Extension of the membrane on the cornea or pressure from the swollen lid may cause corneal opacity and blindness Ocular diphtheria may be primary and acquired through droplets being thrown into the eye by a diphtheria patient It is more likely to be secondary to infection of the throat and nose

Aural Diphtheria

Diphtheria infection may reach the ear through the eustachian tube or may be carried to the ear from the outside The membrane may extend out along the auditory canal and appear on the concha The appearance of this membrane may give the first inkling of the diphtheritic nature of the disease Most of the otitis media is however a secondary infection although the discharge may contain virulent diphtheria bacilli for long periods That these are not the cause of the infection may be shown by a negative Schick test or by the use of antitoxin as a therapeutic test

that in any way interfere with breathing, he does not eat or drink because of the insistent demand on the breathing center The thirst often becomes extreme and the patient reaches out with avidity for the glass only to drop it after putting it to the lips The face is cyanotic and often bathed with perspiration

When the membrane forms chiefly in the trachea and lungs the signs may be very slight until the sudden separation of membrane produces alarming dyspnea In one of the most extensive of my cases the only sign for 10 days was a slight infrequent croupy cough Then a severe strangling spell occurred and a large tracheal cast was expectorated When the patient was first seen the membrane extended from the tip of the epiglottis downward to the smaller ramifications of the bronchi Casts of the primary bronchi had to be removed by bronchoscopy to relieve obstruction at the bifurcation

Following expectoration of the cast the patient may be greatly or entirely relieved If the disease has not stopped however the membrane may be rapidly replaced and may be again expectorated The loosening of the membrane from the trachea or larynx may produce very sudden and alarming dyspnea and if not relieved lead to rapid death Without doubt infection of the larynx may run a mild and favorable course and spontaneously recover, but this is very improbable and progressive increase of the signs is the rule

After intubation the course may be perfectly favorable or casts of membrane may obstruct suddenly the tube A flap of membrane may produce a valve action so that air can enter but not leave with consequent emphysema and if unrelieved death ensues A piece of membrane may be over or against the tube in such a way as to produce a marked reed like sound on expiration Complicating infection may occur especially bronchopneumonia to modify markedly the clinical appearance

Pulmonary Diphtheria

Extensions of the membrane downward through the trachea and bronchi are not very uncommon in laryngeal diphtheria Primary diphtheria infections of the lower respiratory tract are undoubtedly rare although the difficulty in recognition of the disease may be partly responsible In adults the large size of the larynx allows at times a very extensive invasion of the lungs with relatively slight signs referable to the larynx In my experience there has always been the tell tale evidence of larynx involvement to warn the physician of the nature of the disease

The physical signs of this extensive respiratory involvement often are surprisingly little until sudden separation of the membrane from the wall brings on marked stenosis at the bifurcation or above Detachment of the membrane below the bifurcation may cut off the whole or one of the parts of the lung from respiratory function

In one of my cases a physician with tracheal involvement the whole right lung showed practically no respiratory murmur and when the patient turned on the left side severe dyspnea and coughing would appear due to the membrane dropping across the left bronchus as well Recovery was rapid and complete The onset had been a week earlier with cough lassitude and hoarseness and had led to the suspicion of tuberculosis The sudden attack of severe coughing was attended by expectoration of membrane

Whether diphtheria itself causes pneumonia in the pulmonary cases it is difficult to be sure Certainly diphtheria infection occurs low in the respiratory passages and bronchpneumonia merge with the laryngeal and tracheal picture Other organisms are invariably present however, and many of the broncho-pneumonias occur as the diphtheritic process is clearing and the patient is immune At times the pneumonia rapidly clears with the faucial diphtheria and points strongly to the possibility of a diphtheritic process The large amount of antitoxin required in such cases to secure clearing of a relatively mild throat infection also is suggestive

Ocular Diphtheria

Infection of the conjunctival sac occurs infrequently probably because of the protective mechanism and the less frequency with which infection may be carried to the eye as compared to the nose and throat When infection does occur it is of great importance because of the rapidity with which it may lead to blindness Rapid swelling of the conjunctiva occurs with puffing of the lids and a thin seromucoid discharge The membrane appears at first as a thin gray layer but may rapidly increase and become fairly thick Extension of the membrane on the cornea or pressure from the swollen lid may cause corneal opacity and blindness Ocular diphtheria may be primary and acquired through droplets being thrown into the eye by a diphtheria patient It is more likely to be secondary to infection of the throat and nose

Aural Diphtheria

Diphtheria infection may reach the ear through the eustachian tube or may be carried to the ear from the outside The membrane may extend out along the auditory canal and appear on the concha The appearance of this membrane may give the first inkling of the diphtheritic nature of the disease Most of the otitis media is however a secondary infection although the discharge may contain virulent diphtheria bacilli for long periods That these are not the cause of the infection may be shown by a negative Schick test or by the use of antitoxin as a therapeutic test

Cutaneous Diphtheria

Diphtheria of the skin occurs only on areas previously injured as wounds abrasions scratches burns sinuses impetigo varicella dermatitis eczema lupus vulgaris etc It may be primary of the skin or follow diphtheria of the mucous membranes In several cases coming under my observation the cutaneous diphtheria has been the source of secondary diphtheria of the mucous membranes and of diphtheria in other members of the family In these cases the trivial but persistent abrasion of the hand had not been suspected by the family

The appearance varies with the severity extent and duration of the process and the nature of the predisposing injury There is usually a grayish membrane simulating a slough with seropurulent discharge, some redness and swelling and a tendency to excoriation of the surrounding skin In some cases of less virulence a yellowish or brownish crust forms on removal of which a grayish granular and slightly excavated area is seen In other cases the membrane may be very extensive and thick and closely approach the appearance of diphtheria in the throat In one fatal primary case the membrane covered an area of dermatitis about the groins and abdomen of over 25 square inches Skin diphtheria is commonest about the face next on the hands and rare on other parts It may extend from the middle ear and appear on the concha or behind the auricle

Toxin absorption is slow and usually unimportant and very extensive involvement is necessary to approach the toxic dangers of moderate nasopharyngeal cases These cases heal rapidly with antitoxin treatment Because of the frequency of diphtheroid bacteria in the skin it is essential to demonstrate that the diphtheria bacilli in these cases are virulent and that the patient is susceptible by means of the Schick test as well as having the therapeutic test of rapid cure with antitoxin alone

Wound Diphtheria

The diphtheria infection may be obscure the appearances being modified or overshadowed by other attending or preceding infection The membrane rarely has a similarity to that of the throat but appears more like a slough There may be profuse discharge and swelling and there is no obvious cause for the lighting up or continuance of the inflammation Cultures usually are necessary for the recognition of the diphtheria The course often is prolonged, tending toward a persistence rarely if ever seen in the faucial type Paralysis of nerve trunks adjacent to the wound may occur but rarely is generalized

In the tropics extensive ulcerations of the skin are ascribed to diphtheria The frequency with which skin infection occurs in tropical conditions due to moisture heat and trauma may be a factor During the war especially extensive

lesions ascribed to diphtheria have been reported Some cases develop sensory and motor neuritides It is often difficult without special studies to determine in which of these cases diphtheria is significant although it is clearly not frequently if ever the primary difficulty

Diphtheria of the Genitals

Diphtheria of the glans or prepuce either spontaneous or following circumcision occurs rarely The infection usually is secondary to throat or nose but some have been primary The appearance is that of infection with discharge membrane deposit and considerable swelling There is usually no pain on micturition and the urine is normal

Vulvar infection has occurred through inoculation of a simple vulvitis or secondary to varicella Moisture and heat tend to favor localization here and itching leads to inoculation with infected fingers Swelling and tenderness with redness discharge and membrane deposit are fairly typical features There may be painful micturition but bladder involvement has been lacking In the puerperium diphtheria of the vagina and even of the uterus may occur but is very rare

Oral Diphtheria

Oral diphtheria is relatively rare The infection occurs on the tongue and buccal mucosa only after some injury as carious teeth stomatitis trauma etc It is usually local and mild and of little clinical importance I have never seen diphtheria of the mouth alone and membrane here must be accepted as diphtheria only after careful study On the lips diphtheria membrane may cover much of the vermilion area Many of the membranou cases of the mouth and lips show no diphtheria bacilli and some are due to deficiencies in the vitamin B complex

Other Localizations of Diphtheria

Esophageal diphtheria rarely is seen clinically possibly because of the infrequency of esophageal examinations I have seen well marked involvement of the beginning of the esophagus with dysphagia but in many hundred laryngoscopic examinations the esophagus has been negative Diphtheria of the stomach rarely can be recognized during life although it has been found post mortem In one of my cases severe vomiting and prostration were present entirely out of proportion to the faucial involvement and the patient died on the fifth day The gastric mucosa showed great redness and superficial ulceration of the rugae and

diphtheria bacilli were obtained from the lesions The throat had cleared, however and no characteristic membrane could be made out in the gastric lesions

Diphtheria of the intestines and bladder has not been observed In membranous colitis large casts may be expelled, but in no case has true diphtheria been shown Conradi and Bierast and others have reported diphtheria bacilli in the urine in a large percentage 30 per cent of cases, and Byer reported that of 8 cases in which virulence was tested 6 were virulent These results are at variance with the infrequency of diphtheria of the genitals and the rarity of bacteriemia in this disease and further study is desirable

Malignant Diphtheria

The appearance of the malignant case is striking rapid swelling of the throat and neck sometimes with very thick membrane forming profuse seromucoid nasal discharge and obstruction if the disease has attacked the nose dysphagia and dyspnoea if the throat is markedly obstructed, and oozing or severe hemorrhage into the tissues or from the surface The local and general appearances are in entire keeping with the diphtheritic process and do not suggest any action by other organisms as streptococci The course and complications in the main follow this also What is responsible for this extreme virulence is unknown It was thought recently that it was due to some peculiar type gravis although how was in dispute It seems at present improbable that these severe cases can be connected with any one known type The influence of other organisms like streptococci to act by synergy the development of strains which produce toxin well in spite of relatively high iron concentrations etc are suspected but not sufficiently extensively proved

Statements by clinicians that some cases are not acted on by antitoxin seems very unlikely All toxins so far produced have been identical in combining with antitoxin although avidity may be a factor It must be remembered that antitoxin does not stop the disease process in itself It combines with free toxin to prevent further disease and toxin already fixed may continue the inflammation for 36 to 48 hours Fatal poisoning occurs in about 24 hours in some cases Therefore it is clear that deaths at times are sure to occur in malignant cases treated on the 2nd day or later What significance Ipsen's studies will prove to have is entirely uncertain

Complications

The most important complications paralysis and acute cardiac insufficiency are the result solely of diphtheria toxin and therefore, as characteristic of the disease, or even more so as the acute and local signs Their appearance in the convalescence however has led them to be classed with the complications

Diphtheritic Paralysis

Diphtheritic paralysis is due to a toxic degeneration of the peripheral nerve the cell escaping The paralysis is transient and without residuals is incomplete in practically every involved nerve and is likely to be of widespread distribution Both motor and sensory fibers are involved but the sensory are much less susceptible so that while motor paralysis is frequent and often alone sensory paralysis is only seen when motor paralysis is present and usually appears a little later

Paralysis usually occurs in the severe toxic cases with great swelling and extensive membrane and where antitoxin has not been given early The pharyngeal and nasopharyngeal cases chiefly suffer, as absorption from the anterior nares and the larynx and trachea is too slight frequently to cause this complication Mild throat cases may however absorb enough toxin to cause paralysis if untreated or treated too late

Paralysis is preventable only by early administration of antitoxin in sufficient amount From a large experience one must acknowledge that in severe types large doses during the first day only will entirely prevent paralysis and that in one or two days without question sufficient toxin may act on the nerve to produce this complication although in many cases it may be prevented by somewhat later treatment Paralysis never results from antitoxin although the layman often so thinks because of post hoc reasons

The insidious onset and incompleteness of the paralysis make the time difficult of accurate determination The earliest appreciable paralysis in my cases was on the fifth day involving the palate The latest that paralysis may first appear is the sixth to seventh week Slight degrees of paralysis however often are overlooked and marked paralysis may first be noticed as late as the eighth to tenth week It is probable that in all cases some paralysis has occurred before the end of the fourth week although it may not have been demonstrated A striking progression of the paralysis in faucial diphtheria often occurs appearing first in the throat then eyes face larynx neck arms trunk and legs and clearing in the same order so that at any one time only one location may show marked paralysis Although paralysis is clearing or has cleared in one area like the throat it may still appear and progress to a marked degree in other areas as the extremities In severe cases paralysis may extend for 2 to 3 months after the sore throat

In most cases the paralysis appears in the second or third week and lasts 1 to 8 weeks depending on severity The paralysis usually shows a gradual increase for from 1 to 8 weeks until the maximum is reached and then more rapidly subsides The whole duration may be weeks to 3 to 4 months Recurring paralysis has been observed only in the palate in faucial diphtheria appearing

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ataxia Romberg s sign and loss of knee jerks Paralysis of smooth muscle apparently never appears as a diphtheria paralysis and sympathetic system involvement has not been demonstrated Hemiplegia and monoplegia of central origin may occur during diphtheria but they are rare and are due to cerebral hemorrhage or thrombosis and not directly to the diphtheria toxin They, of course may persist in contrast to the diphtheritic paralysis

Cardiac Involvement

The characteristic cardiac disturbance is a neuromuscular deficiency and is shown by various types of arrhythmia and circulatory changes The onset usually is during the second week of the disease when convalescence is apparently well under way but it may appear as late as the end of the third week The onset is sudden as a rule with listlessness vomiting and pallor as the characteristic signs but rarely may be slower and more insidious The patient may deny any discomfort but be disinclined to activity or to eat and object to any disturbance There may be marked irritability In all severe cases there are epigastric pain and distress with tenderness along the whole liver edge which usually is down

Vomiting occurs in 75 per cent of the cases and always in severe cases It is often projectile and persists as long as anything is taken by mouth There is no distention of the abdomen but usually there are pain and tenderness in the epigastrium with voluntary spasm Pallor is one of the striking early signs The skin is pale and the extremities slightly cool The lips are grayish The mind is clear but usually there is great listlessness or restlessness and irritability

Arrhythmia is the most typical of the physical findings This is present as soon as the above symptoms are present There may be softening of the first sound preceding the arrhythmia for a day or two Two main types of arrhythmia occur gallop rhythm either with 3 or 4 sounds to the cycle and partial or complete heart block In the cases with gallop the rate may remain normal but usually is increased to 110 to 140 or rarely more The blood pressure is low and the pulse thin thready and sometimes impalpable In the block cases the pulse is usually from 30 to 40 There may be rapid and frequent changes in the rhythm so that in 24 hours all types of arrhythmia may occur including flutter and fibrillation There is no edema no dyspnea and rarely cyanosis

Electrocardiograms are most satisfactory for demonstrating cardiac damage and the most extraordinary changes may occur In the mild and favorable cases the changes are chiefly in reduced voltage and reduction or inversion of the T waves A V block or dissociation may be complete although alone not usually dangerous In one case only in the South Department following diphtheria complete A V block occurred which has persisted now for 40 years The patient has shown no circulatory deficiency

at the end of the first week, increasing for a few days and subsiding within 1 to 2 weeks the recurrent paralysis has appeared in the third or fourth week and gone through a course somewhat longer The probable explanation is that the early paralysis is due to toxin injury to the nerve at or near the end plates from toxin directly in the tissues during absorption, and that the later paralysis is due to toxic injury higher up and due to blood distribution of toxin

Frequency of paralysis varies with the severity of the cases the efficiency of antitoxin treatment and the care used to detect the condition

Palatal paralysis the most frequent and earliest, presents nasal voice and regurgitation The voice defect may be easily heard in ordinary conversation when marked and may make the patient's talk almost unintelligible The words 'plum pudding are used to elicit it in my wards, and any lingual or explosive sounds may be used The palate lies flaccid or, if the paralysis is unilateral, it may be pulled to one side on raising it Whistling or puffing out the cheeks may be impossible Sensory involvement may occur so that the pharyngeal reflex is lost or diminished

Constrictor paralysis causes difficult swallowing of solids and perhaps less so of liquids Severe choking may occur on pieces of meat bread candy etc and fatal asphyxia has resulted When extensive swallowing may be impossible There is a distressing hollow ineffectual cough with rattling in the throat of mucus and saliva which the patient is unable to raise accompanied by great weakness and prostration producing a typical and alarming picture

Laryngeal paralysis produces a change in voice either lower or higher pitched or weak and aphonic Difficult breathing from abductor paralysis rarely occurs After laryngeal diphtheria loss of voice or persistent stenosis usually is due to change in the mucous membrane caused by infection pressure or trauma rather than to toxic nerve injury Ocular paralysis may be either of the ciliary or of the extrinsic muscles Motor paralysis of neck trunk and extremities occurs and produces a corresponding disturbance of function

Paralysis of the respiratory muscles is the only dangerous or fatal form aside from the cardiac injury It may involve the phrenic nerve with loss of power of moving and fixing the diaphragm producing severe and often fatal dyspnea or it may involve the accessory muscles so that respiration has to be done by the diaphragm alone Varying degrees and combinations of course occur The respiratory paralyses usually occur from the third to the eighth week

Sensory paralysis may show loss of tactile sense or pain sense or both Pain sense, especially, may be lost while tactile sense remains Loss of the pharyngeal reflex occurs usually in the second week The sensory involvement of the extremities occurs late usually 5 or 6 weeks later Numbness and tingling may occur I have never seen temperature sense lost but the muscle sense may be affected markedly These patients may have the typical tabetic picture with

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intubation especially where there is severe coughing It is found usually at the base of the neck but may spread to face chest back and at times over most of the body Cervical adenitis is not rare It usually involves the lymph nodes at the angle of the jaw Suppuration may occur The course and outcome usually are favorable Deep cellulitis of the neck is infrequent and erosion of the deep vessels as seen in scarlet fever and septic throats is practically never seen Sinusitis probably is not infrequent but is not readily noted in most cases

Diagnosis

Diagnosis is to be made clinically chiefly on the characteristics of the local inflammation as the constitutional signs usually are mild and not distinctive and are subject to great variation There is often great difficulty in the clinical differentiation and the diagnosis must often be made with reservation Fortunately the application of treatment antitoxin need not wait upon final or accurate diagnosis as it has no unfavorable effect on nondiphtheritic infections while early use is especially important in diphtheria

Cultural diagnosis has been of enormous aid in the diagnosis of diphtheria It has greatly clarified the diagnosis so that we may recognize clinically with considerable accuracy cases which before bacteriological aid were diagnosed erroneously such as the streptococcic cases Vincent s angina follicular types etc It has brought the recognition of the mild catarrhal cases and the detection of the carrier

The cultural diagnosis must not be taken however as an absolute measure of a correct diagnosis Its defects will be considered later To be of value cultural diagnosis must be carried out carefully and careless and haphazard methods make it more harmful than helpful The following points are essential to consistent results

1 The swab must be thoroughly but gently rubbed over the infected area It is well not to touch other areas In the throat this requires a good illumination and cooperation of the patient otherwise he must be restrained and a gag may be necessary With practice good results may be secured with a minimum of discomfort to the patient When gagging or other interference interrupts the careful swabbing it may be desirable to repeat The culture is too important to let the feelings of the patient influence the technique greatly If the membrane is very thick it is often better to swab the edge of it rather than the center If the culture is to discover a carrier all areas which might harbor the organisms must be swabbed as both tonsils the pharyngeal wall the nasal cavities and other areas such as wounds aural discharge skin etc if there is inflammation in which the organisms might persist The swabs from these various areas should be planted separately In primary laryngeal cases accurate results

Myocarditis is a striking feature, and in fatal cases a large proportion of the muscle fibers may show fatty degeneration Acute dilation may be slight or very marked with weakening of the sounds

The course of cardiac disturbance is rapid Death often occurs suddenly, in from 1 to 7 days rarely later after appearance of symptoms Unless carefully watched death may occur at times apparently without warning The mortality of this complication varies from 50 per cent to 100 per cent In most cases that survive a week or 10 days recovery occurs In the favorable cases cardiac signs and general symptoms disappear with rapidity after a few days, and the heart returns to normal Muscle weakness may persist for weeks, but the arrhythmia is absent Periods of arrhythmia and normal rhythm may alternate for a number of days and rarely for to 3 weeks

The rapid clinical recovery of the cardiac cases that escape death is one of the striking features of the disease Late muscle weakness in the fifth to sixth week is present at times even in cases that failed to show any of the signs of the acute cardiac disturbance Acute dilatation and sudden death may occur on exertion These late effects usually are associated with late paralysis and yield the usual signs of weak cardiac muscle power In my experience these late cardiac deaths never occur if the patient is kept at rest for a suitable period The final outcome of the diphtheria heart in non fatal cases clinically is excellent Although severe fibrous myocarditis might be expected to result, I have never found it in the usual clinical examination

Endocarditis with myocarditis is rare and undoubtedly results from secondary infection rather than from the diphtheria bacillus Diphtheria bacilli have been reported from the heart lesions but not alone and no connection with the disease has been shown The endocarditis usually occurs during the convalescence at a time when the patient is immune to diphtheria and besides it is less frequent than in other sore throats as tonsillitis and scarlet fever

Other Complications

An actual nephritis is an occasional complication Anuria is rare Acute otitis media is a common complication It is due to the pus cocci especially the streptococci but diphtheria bacilli may be present In all cases cultures should be taken from the discharge before release Acute arthritis is a rare complication after diphtheria and in some of the cases from history and course is apparently a coincident rheumatic arthritis Lobar pneumonia is very rare and probably does not occur more often than in healthy children Bronchopneumonia may occur in the severe faucial cases and is especially characteristic of the laryngeal cases being responsible for 75 to 80 per cent of all the deaths of this type Cutaneous emphysema may occur in laryngeal stenosis either before or after

syphilis of the throat in Vincent s angina and in tonsillitis The e instances are rare exception however and no clinician of judgmen would fail to treat as diphtheria inflammations from which diphtheria bacilli were obtained The cultural diagnosis has been of great value in improving the clinical diagnosis in the recognition of early cases before characteri tic signs have developed in the recognition of atypical ca es either very mild or very severe and of those complicated by other infections as scarlet fever and in the discovery of carriers Cultures should be taken from every case showing infection of the mucous membranes The physician who neglects to do this as a routine will certainly have occasion sometime to regret it

Because of the saving of time examination of smears of material direct from the tissues is often of value The diagnosis from these is somewhat less accurate than from the culture as the organisms may be very few the morphology less typical and confusion may occur with other organisms which would not appear in culture The smear examination should always be confirmed by culture

In clinical diagno is apart from bacteriological diagnosis chief dependence should be placed on the character of the inflammation as already described Toxic symptoms as a rule are slight and may be practically absent Severe toxic symptoms as high fever marked malai e backache and muscle ache severe vomiting delirium or coma throw doubt on diphtheria but do not exclude it The great variation in the disease mu t be constantly in mind and although the larger number of cases can be recognized clinically without great difficulty some are impos ible of ready diagnosis Many children do not complain of sore throat at the beginning and only routine examination of the throat will lead to prompt diagnosis I have repeatedly found well marked diphtheria in children who e mothe s did not know they were sick No physical examination should lack an examination of throat and nose

Differential diagnosis should consider a large variety of conditions Streptococcus sore throat is one of the most difficult di eases to differentiate when it shows membrane as often is the case In it the toxic symptoms u ually are more marked with high fever headache backache bone pains malai e vomiting and nervous symptoms In some cases however differentiation is impossible and in any case where doubt occurs the patient hould be given the antitoxin treatment

Simple tonsillitis usually offers no difficulties Vincent s angina always is characterized by ulceration which is the ine qua non of diagnosis The ulcer often is so filled with the necrotic exudate as to simulate closely diphtheritic membrane but careful observation of the whole margin usually will demonstrate that the exudate is not laid on or swabbing will show the necrotic nature of the lesion by removing masses of the exudate Bleeding often occurs on such swabbing Redness is charac teristically slight and limited to a narrow zone around

can be obtained only by taking the swab direct from the larynx This is best done through a laryngoscope In postnasal cases the swab may be passed up from the throat or along the floor of the nose Cultures should not be taken immediately after the use of antiseptic gargles, sprays or lozenges

2 The media should be thoroughly inoculated by gently rubbing the swab over it so that it is well planted

3 The media must be suitable for characteristic growth and morphology of diphtheria as Loeffler s blood serum, it must be moist Tellurite media in experienced hands gives more accurate results

4 Incubation should be for 12 to 18 hours and at 35° to 37° C While shorter incubation often may be used, error is greater, and the result should be controlled by reincubation

While most of the errors in bacteriological diagnosis may be excluded by proper care it must not be forgotten in practical work that a negative culture may be reported from a diphtheria case and at times a positive culture from a patient not actually infected with the disease Failure to spread properly in inoculating the tube with the swab poor growth and poor bacteriological diagnosis are factors which may cause error

Quick cultural diagnosis either by direct smear or Bradhy s swabs, etc while of interest and of some value should be used with great care The exclusion of diphtheria by this means is uncertain In any case, in which such means might be of value it is better to treat the case promptly as diphtheria, leaving the final bacteriological diagnosis for later Manzulla devised a tellurite test in which 2 per cent potassium tellurite solution freshly made within a month is applied to a suspected membranous disease In 10 minutes diphtheritic lesions become blackened or grayish Peroxide tannic acid or methylene blue may give false results While diphthereal lesions usually are positive other local infections frequently may give false reactions

It is unsafe to accept a negative culture as excluding diphtheria when the clinical signs are definite This has been shown repeatedly to the chagrin of the physician and the danger of the patient Cultures should be repeated if negative whenever there is ground to suspect diphtheria using care to exclude all possible errors Diphtheria carriers also may show the presence of *C diphtheriae* intermittently due to the focus being in the sinuses of the nose or the depths of the tonsillar crypts or in other inaccessible places from which the organisms are thrown out from time to time

It must be acknowledged that the presence of virulent diphtheria bacilli in lesions of the mucous membranes which simulate diphtheria does not prove that the patient has this disease This has been shown by means of negative Schick tests by clinical course and by reliable evidence of the true nature of the infection For example diphtheria bacilli have been found in uncomplicated

of the gums the odor is foul dysphagia sometimes is marked and there is no fever The absence of history of the use of mercury may be becau e the patient does not appreciate the absorption from the skin or because of a desire to conceal its use Of the cases in my wards 2 had used bichloride by vagina and 1 by mouth for abortion 2 had taken the drug by accident or with suicidal intent and 1 had used mercurial ointment for extensive pediculosis of the pubic type

In occasional cases in infants sufficiently large masses of thrush infection have oc urred on the tonsils to suggest diphtheria In various infections and toxemias as typhoid pneumonia meningitis etc where mental torpor mouth breathing or fluid limitation is present sticky non membranous exudates may be spread over the mucosa and simulate diphtheritic membrane In these cases the toxic symptoms are more severe than usually seen in diphtheria and the exudate wipes off has no structural relation to the underlying tissue and shows no mem branous form as in diphtheria

Differential diagnosis of nasal diphtheria requires the consideration of all conditions with nasal discharge or obstruction foreign bodies sinus infection syphilis caries of the vomer rhinitis etc may simulate it Before the Schick test the diphtheritic nature of the process even when showing diphtheria bacilli could only be shown by the therapeutic effects of antitoxin Now diphtheria carriers suffering from other causes of nasal discharge and obstruction may be recognized by negative Schick tests

The differential diagnosis of laryngeal diphtheria often is difficult Obstruc tions above the larynx below the larynx and at the larynx may be due to diph theria and therefore dyspnea due to any of these causes as well as toxic dyspneas must be carefully considered The great seriousness of these cases the im portance of early antitoxin and the need of mechanical relief fitted to the condi tion make diagnosis of tremendous importance In general obstructions above the larynx as of the pharynx or involving the epiglottis and laryngeal atrium pro- duce an *inspiratory* dyspnea obstructions at the larynx such as the usual case of diphtheria produce both an inspiratory and expiratory dyspnea with little difference in degree while obstructions below the larynx as foreign bodies at the bifurcation of the trachea produce chiefly an *expiratory* dyspnea Retrophar yngeal abscess phlegmon of the epiglottis spasmodic croup various types of obstruction and status thymicolymphaticus must be considered

Spasmodic croup is distinguished by sudden onset (or subsidence) especially at night by being precipitated by any mild infection as a cold by lack of dysphonia by a familial history and previous attacks and on laryngeal examination the absence of pseudomembrane or mechanical obstruction

Foreign body produces a sudden strangling attack at time of lodgement If the infant is not seen however during lodgement and the foreign body does not itself cut off the passage this strangling attack subsides in several minutes to be

the ulcer and lymph node reaction in the neck usually is absent Secondary infection with the streptococcus may lead to marked redness, swelling and adenitis but such signs throw doubt on the Vincent's angina The exudate has a very foul odor and a similar odor is found in cultures of the *Bacillus fusiformis* Smears of the exudate especially from the deeper layers, stained with any intense basic stain as gentian violet show the fusiform bacillus and the long wavy spirochete often to the exclusion of other organisms The presence of such organisms in smears cannot be accepted alone for diagnosis, as they may be found at times in diphtheria and often in dirty mouths

In peritonsillar abscess before fluctuation has appeared the swelling must be distinguished from phlegmonous diphtheria Many cases of this type of diphtheria have come under my observation where incision has been made with disastrous results In peritonsillitis the greater brilliancy of the redness the greater tenderness and difficulty of opening the mouth the harder infiltration and the more marked general symptoms usually will differentiate Again the importance of routine culturing and of prompt administration of antitoxin in case of doubt should be emphasized as the phlegmonous case of diphtheria invariably is severe

The mucous patch of syphilis may suggest diphtheria at first glance and error in diagnosis has been made The lesion is however a necrosis and not a laid on membrane the margin is apt to be irregular and shade into the normal tissue and the more frequent mouth involvement may be suggestive The duration usually may be found to have been weeks and other evidence as roseola general adenopathy periostitis or the remains of the chancre may clarify the diagnosis In other forms of syphilis confusion is not probable

The confusion of scarlet fever with diphtheria is due to the streptococcus membrane formation Injuries to the throat, as tonsillectomy incisions etc produce membrane like areas which often are confusing In some of these the form location or margins of the lesion will make the diagnosis clear The loss of tissue absence of extension surrounding redness and history usually will aid recognition Diphtheria occurring immediately after tonsillectomy or incision may be easily overlooked and I have seen many cases where the true nature of the condition was unnoted until the larynx became infected Culturing of the throats before and after tonsillectomy would have been of great value in some of these cases

The whitish patches often extensive in mercurial poisoning may simulate diphtheria very closely Seven such cases have been referred to the South Department as diphtheria The membrane like deposits are really necroses instead of the laid on fibrinous membrane of diphtheria and tend to merge with the surrounding mucous membrane and show greater irregularity in contour The mouth frequently is affected often there are salivation and ulceration and swelling

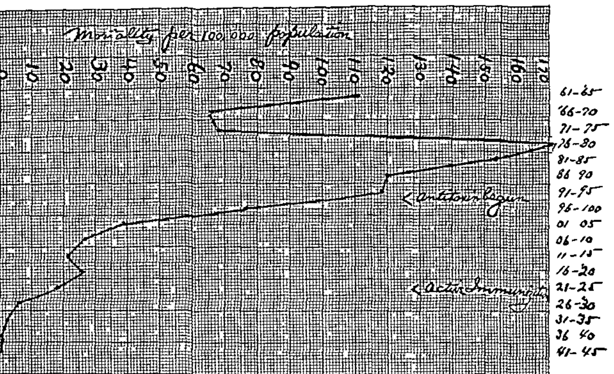


FIG 1 Diphtheria mortality in Boston per 100 000 population from 1861–65 to 1941 45 *Antitoxin began to be used in 1895* and active immunization in the period 1921–5

followed by the usual signs of partial obstruction stridor dysphonia or aphonia and possibly dyspnea With settling of the foreign body or its irritation producing swelling there may succeed the progressive course seen in infection as diphtheria Radio opaque bodies can be diagnosed by x ray, laryngoscopy serves for the diagnosis of any foreign body Cases occasionally are sent to hospital without suspicion of a foreign body which is found there on routine laryngoscopy

Other acute infections usually are only to be differentiated by laryngoscopic appearance and laryngeal cultures Subacute and chronic obstruction as from tuberculosis or syphilis gives a slower, more prolonged duration than is seen in diphtheria

Spasm of the larynx may occur from brain infection producing irritation of the recurrent laryngeal nerve center in the medulla as rarely seen in poliomyelitis or in tabetic laryngeal crisis

Inspiratory laryngeal spasm crowing inspiratory stridor may occur in tetany No cough or aphonia is present and rickets usually is evident Edema of the glottis from allergy angioneurotic edema is reported, but in none of these cases has actual obstruction from swelling of the laryngeal mucosa been seen by us

Acute edema from injury should be recognized Severe throat infections may occur with a marked fluid infiltration of the epiglottis and aryepiglottic folds producing the picture of phlegmon

Phlegmon of the glottis due to supraglottic cellulitis often is very rapid in its course is associated with high temperature and marked inspiratory stridor but usually there is no cough and no aphonia Palpation with finger readily shows the swollen epiglottis This condition may rapidly require tracheotomy or lead to death by septicemia

Toxic dyspnea as in pneumonias acidosis or poisonings is to be distinguished *from obstructive dyspnea chiefly by the absence of stridor or other* laryngeal sign as croupiness as well as by the demonstration of the cause of the dyspnea Asthmatic breathing has a prolonged expiratory stridor but no croupiness or aphonia

Prognosis

The course of diphtheria is especially treacherous so that in any given case the prognosis must be given with caution Mild cases usually do perfectly well and the severe cases show obvious cause in the local inflammation for anxiety *to those familiar with the disease* Cases that locally seem *mild however* at times show very great toxic after effects

Antitoxin has an enormous effect on the mortality so that prognosis cannot be considered properly except in the light of antitoxin treatment (see Fig 1 and Tables III and IV) In cases in which antitoxin has been administered

TABLE IV

MORTALITY IN INTUBATION CASES

	Cases	*Mortality Per Cent*	
1888	100	78	Boston City Hospital (In 1888 a diphtheria ward was opened)
89	128	81.25	
90	93	84.9	
91	50	84	
92	65	86.1	
93	109	82.5	
94	89	83.1	
1895	118	54.2	South Department of Boston City Hospital (In 1895 antitoxin began to be used in same year South Department was opened at Boston City Hospital for care of contagious diseases)
96	2 4	[illegible]4.7	
97	146	45.9	
98	71	59.1	
99	192	32.8	
1900	59	33.6	
01	184	31.5	
02	145	33.8	
03	139	26.6	
04	153	30.7	
05	135	25.9	
1906–1910	914	18.8	
1911–1915	666	22	
1916–1920	756	23.5	
1921–1925	5 8	31.5	
1926–1930	9	21.5	
1931–1935	8	15.4	
1936–1940	58	26	
1941–1945	40	12.5	

Note.—These figures include all acute laryngeal infections requiring intubation exclusive of measles

more important A connected bathroom simplifies the technique The simpler the furniture the better The nurse or attendant should wear a gown and avoid carrying the infection on her clothes The hands should be washed carefully on leaving the room and care must be used about door knobs Dishes may be kept with the patient the food from the kitchen dishes being transferred without contaminating them or after use the dishes may be put into a clean kettle outside the infected zone covered with water and then the kettle may be removed for boiling without the outside being contaminated Linen may be treated similarly The easiest way is to carefully deposit the linen in a clean bag which has not been contaminated on the outside This may then be carried off and boiled in toto Papers waste etc may be deposited similarly in clean paper bags and these removed and burned without opening

TABLE III

PER CENT MORTALITY OF DIPHTHERIA BOSTON CITY HOSPITAL

	Cases	Mortality
1888	362	46
89	529	45 1
90	415	36 3
91	237	41
92	387	47 8
93	419	48 4
94	698	38 1

ANTITOXIN USED

	Cases	Mortality
1895	1455	14 2
96	1889	14 6
97	1381	13
98	817	11 8
99	1621	9 9
1900	2547	11 5
01	1576	11 7
02	1008	10 2
03	1179	11 7
04	1431	9 5
05	866	9 4
1906–1910	6749	7 8
1911–1915	6080	8 4
1916–1920	6369	8 8
1921–1925	3 40	11 7
1926–1930	1329	8 9
1931–1935	517	8 1
1936–1940	158	4 4
1941–1945	133	6

early the death rate is practically zero but with every day of delay in the use of this remedy the mortality mounts by leaps and bounds

PROPHYLAXIS

Of the means now available for prevention we have isolation and disinfection discovery of the carriers by culturing personal hygiene and immunizing

Isolation — The methods of isolation must be fitted to the special circumstances The room should be sunny if possible and a balcony is advantageous It is not necessary to have the isolation room located at the top of the house as was formerly advised but ease of access and completeness of the asepsis are

2 doses at intervals of 3 to 8 weeks. Three doses of soluble toxoid (Ramon) at intervals of 3 or more weeks is of about equal value. Immunity develops in to 3 months in 95 per cent and may be increased to nearly 100 per cent by reimmunizing the susceptibles.

Because of the gradual loss of immunity and the decrease in the "natural immunizing" community factors, it is desirable to give a booster of 0.2 to 0.5 c.c. at intervals of 3 to 5 years, or when there is prevalence of diphtheria. Rapid immunity within 10 days results from these booster doses in immunized children. Few of the diphtheria cases now seen occur in immunized children and in these usually no immunity was ever demonstrated.

All children should be immunized during their first year. It is now customary to use combined immunization of whooping cough and diphtheria and also tetanus toxoid, which has been shown to be highly efficient.

While making throat cultures of contacts and of suspected carriers and isolation of infected persons, etc., still should be carried on, it is far more important to put the chief investment in immunization.

Treatment

In but few diseases at present can the science of medicine point with such pride of accomplishment in treatment as in diphtheria. With suitable and obtainable antitoxins we have a sure cure, a certain preventive and reliable means of detecting all the sources of the disease. If carelessness, ignorance and inertia were excluded, the death rate today could be zero and without any revolutionary changes in the environment or daily routine of the world. That the present death rate still ranks high in the infectious diseases is a disgrace to civilization.

Antitoxin Treatment

Antitoxin acts as a pure antidote, neutralizing the toxin but having no direct effect on the bacilli. The antitoxin does not cause the clearing of the inflammation except that it stops action. The presence of antitoxin in the blood and tissues even in large amounts causes no changes that are appreciable, and in treatment there is no need of "balancing" the antitoxin and toxin. An "overdose" of antitoxin does no harm, and in fact every treatment dose must be an overdose in the sense that more antitoxin than chemically needed to neutralize the toxin is given.

Early administration is of first importance in antitoxic treatment. So rapidly is toxin produced and its action accomplished that treatment later than the first day may at times prove too late. Smaller doses also are sufficient in the earlier stages. In case of any doubt in early cases of mucous membrane infection it is

Isolation should be carried out until the patient has been demonstrated free of contagion Two or preferably more consecutive daily cultures from throat and nose as well as any other area in which diphtheria bacilli might be present should be secured before release Because of frequent intermittency, I require 7 consecutive daily cultures before the release of carriers Even these precautions at times fail to prevent the spread of the disease

On releasing the patient it is customary to give him a thorough bath and use fresh clothes Everything in the isolation room should be disinfected by boiling or thorough washing or applications of disinfectants as corrosive sublimate cresol etc or by prolonged exposure to sunlight or strong light and airing the procedure depending on the nature of the material It is not probable however that organisms will survive in the room longer than in the patient s tissues, but such is possible In carrying out the isolation precautions care should be used that as little infection as possible gets about the room This may be done by care in collecting the nasal and other infected secretions on pieces of paper and burning them at once or putting into paper bags In the case of coughing or sneezing the patient should hold a handkerchief or piece of cloth to the face Infected objects should not be spread about more than necessary, and continuous concomitant disinfection thus carried out

Of great importance in prevention are the examination and culturing of contacts every time a case of diphtheria is discovered If thoroughly and efficiently carried out it will do much to prevent the spread of the disease Such contact should be kept as much as possible from others until cultures have proved them free of diphtheria Toys linen handkerchiefs and dishes which may have been used or infected by the patient before the disease was recognized, should be hunted out and disinfected as above

Immunizing — The administration of prophylactic doses of antitoxin 1 000 to 2,000 units will give prompt immunity but often of short duration, as 10 days This short duration of immunity frequently is not understood by the patient who takes no adequate precautions because he thinks himself immune This false sense of safety sometimes is disastrous

The demonstration of active immunization by von Behring therefore has been of great interest The first immunizations were with toxin antitoxin mixtures containing 3 lethal doses of partially neutralized toxin and later, for safety, 0 1 lethal dose

Ramon showed that a toxoid or anatoxin prepared by formalizing diphtheria toxin and incubating until no toxic effect was produced in guinea pigs with 5 cc still retained its immunizing power and could be used in larger dose Glenny first precipitated this toxoid with alum Other precipitants are used as aluminum hydrate

The most efficient immunization is done with precipitated toxoid in at least

if the local inflammation progresses for 24 to 36 hours In former times a second dose or even more would have been given

The experience at the South Department is represented by the following table of dosage

Intravenous

Mild Cases	*Moderate Cases*	*Severe Cases*	*Malignant Cases*
Usually intramuscularly	5 000–15 000	15 000–30 000	60 000–100 000

Intramuscular

Mild Cases	*Moderate Cases*	*Severe Cases*	*Malignant Cases*
1 000–5 000	10 000–30 000	Practically always intravenously 50 000–100 000	Intravenously

Clinical Effect on the Disease —The clinical appearance invariably shows signs of improvement which are rapid and consistent within 36 hours after a suitable antitoxin dose In cases treated early the disease invariably is stopped and if within 24 hours of the onset the patient has always recovered in my experience Persons receiving antitoxin or having antitoxin invariably remain immune while antitoxin persists

The mortality of diphtheria throughout the world before antitoxin was about 30 per cent In the Metropolitan Asylum Board s hospitals for 3 years before antitoxin the mortality was 33 per cent Rosenthal reported in 183 56 cases a mortality of over 38 per cent

Following antitoxin serum disease in its various manifestations frequently is seen Anaphylactic shock must be guarded against by an intradermal or cutaneous test with horse serum When a positive test is obtained desensitization is necessary before treatment with antitoxins

Penicillin

Penicillin has been shown to be usually an effective agent against diphtheria bacilli It cannot be accepted as a valuable treatment without antitoxin and usually is not necessary if antitoxin is given except to reduce the infectious period It is now customary to give penicillin intramuscularly in all malignant cases from 10 000 to 40 000 units every -3 hours or 100,000 units every 8 hours The single daily dose of 300 000 units in wax and oil intramuscularly is used also Oral dosage may be efficient in about 4 times this dosage of intramuscular injection but is somewhat uncertain in its effects Whether this practice materially helps

better to give antitoxin before waiting for final proof, particularly if the inflammation is rapidly increasing

Method of Administration — Antitoxin may be given intravenously or intramuscularly By mouth the action is too slight uncertain and slow to be of practical importance The most rapid action is obtained by the intravenous route so that this is best suited for all severe and advanced cases The discomfort of administration is less and the subsequent discomfort is nil except for the serum reactions There is slightly more serum reaction especially the early chill and fever and it is a somewhat more difficult technique Park has shown that diffusion of antitoxin occurs 10 times more rapidly, when given intravenously than subcutaneously and 4 times more rapidly when given intramuscularly than subcutaneously The usual technique of intravenous and intramuscular injections is followed

Dosage — Some differences of opinion occur as to the amount of antitoxin required for similar cases In Philadelphia and Boston very large doses have been used while in New York much smaller doses prevail The difficulty of determining the optimum dose is due to several factors (1) great variation in the severity of diphtheria poisoning (2) differences in self antitoxin production on the part of the patient (3) administration too late to be effective in any dose (4) the final result in the case may be chiefly determined by the length of time since the disease started rather than the size of dose

There is no doubt that too small amounts of antitoxin still are given frequently while an excessive dose does no harm The chief indication for the size of the dose is the amount of toxin production as shown by the local inflammation If there is rapidly increasing local inflammation especially with swelling or extensive membrane the dose should be large while if the membrane is slight and there are little swelling and slow advance the dose may be small Long duration of the disease indicates larger doses other factors being equal although the probable benefits will be less

The location of the process influences the degree of toxemia faucial and nasal vault infections requiring the largest doses laryngeal infections next and anterior nasal infections the least

The size of the patient affects the concentration of antitoxin in the blood with a given dose but as it also similarly affects the toxin concentration and as younger children have a higher mortality, this has little influence on the dose

The Schick test has given us a valuable help in determination of dosage and to some extent has reduced the dose in severe cases Before the Schick test in the absence of means of showing the time when toxin was neutralized it seemed wise clinically to repeat antitoxin if the disease continued to spread rapidly after 12 hours If the Schick test is done at the time of the antitoxin injection and remains negative it shows that sufficient antitoxin was administered, even

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During the second week of convalescence especially forcing food should be avoided because of the frequency of the acute cardiac disturbance at this time

Hygiene — The importance of fresh air sunshine or good diffused light and cheerful surrounding is considerable The benefit to the general condition from keeping the patient outdoors is very striking and it also relieves the tedium of the long rest in bed

Treatment of Complications

The treatment of the complications is not adequate and certainly here the ounce of prevention is worth many pounds of cure

Cardiac — The most essential treatment is cardiac rest Everything which increases heart work should be reduced to a minimum Rest level in bed with avoidance of effort of the patient in turning or eating and drinking is important Vomiting if present is an indication to reduce the food and fluid by mouth to a minimum or exclude it altogether Severe cases vomit as long as anything is given by mouth The thirst must be relieved by saline enemata or rarely by hypodermoclysis Nutrient enemata of glucose and pancreatized milk may be used Alkalis may be added because of the tendency to acidosis

Of the drugs morphin has proved of greatest value It should be given hypodermically in doses just large enough to secure comfort and repeated often Caffein sodiobenzoate in doses of 0 065 to 0 2 gm (1 to 3 grains) apparently has given some benefit Digitalis in cases showing fibrillation may be of benefit but the type of irregularity is liable to rapid changes On the whole little evidence of the benefit of digitalis has been found in my cases and in those with partial or complete block it is contraindicated

Paralysis — The course of the paralysis usually is favorable Little effects are seen from treatment Thorough massage makes the patient more comfortable Electrical treatment is hardly worth the effort Strychnin sulphate in full doses toward the latter part of the paralysis is of apparent benefit

When the paralysis involves the constrictors of the pharynx care must be used to avoid strangling while eating Liquid food only is often necessary When paralysis is marked stomach or esophageal feeding is necessary The paralysis requires the raising of the foot of the bed 18 to 24 inches and frequent turning from side to side to allow the saliva and mucus to run from the mouth and to avoid hypostatic pneumonia which is so likely to occur Lying on the face is a very good position Atropin may be used to decrease the salivation and when there are moist râles in the lungs Paralysis of the eyes requires no treatment as it invariably disappears

Respiratory paralysis occurs only when there are extensive paralyses elsewhere It is extremely distressing and dangerous A sitting or semi sitting posi

is still uncertain but it reduces the secondary infection and certainly is essential in all laryngeal cases in which pneumonia is the chief cause of death

Local Treatment

Local treatment must be mentioned chiefly to emphasize its uselessness Antitoxin through neutralization of the toxin causes such a rapid and universal improvement in the throat that no other treatment usually is required Before antitoxin while many clinicians had favorite local applications there was very little agreement and a majority of physicians of large experience acknowledged the uselessness of the local treatment Toxin cannot be removed by gargling or mouth washes Mouth cleansing with simple alkaline washes and throat irrigations both hot and cold are often comforting and keep the mucous membranes in good condition Care must be used that gagging is not produced for fear of infecting the ears The irrigation should be done with slight pressure If children fight against irrigations they should not be used The removal of the membrane deposit does not help the patient except for mechanical reasons and it is as well therefore to let it be separated by nature Ice bags to the neck may add to the comfort of the patient Local applications, as iodin methyl salicylate and rubefacients to the neck have no appreciable effect on the disease Local penicillin sometimes is used and may help

General Treatment

The principles of general treatment are rest in bed large fluid intake during the acute stage careful diet and general hygiene

Rest is of special importance as favoring the recovery from the acute disease and decreasing the danger from the complications It should be continued until reasonable surety that the cardiac and paralytic complications will not occur As definite signs of these occur by the fourth to the fifth week patients who have escaped scot free at this time usually may be considered safe In cases of mild or even moderate type when treatment has been given early, patients may be allowed up by the second week but judgment must be used in deciding Severe cases should be guarded especially carefully from exertion until all cardiac danger is past

Fluids — A free fluid intake is desirable in the acute stage In severe cases because of the tendency to acidosis alkalis may be given as sodium citrate and sodium bicarbonate in doses of 0 6 to 2 gm (10 to 30 grains) every four hours

Diet — The diet should be easily digested foods and carbohydrates should predominate Severe cases usually lose considerable weight during the first few weeks, but I feel that it is of doubtful value to try to keep a caloric balance

are immune and the further addition of antitoxin does not aid Immunization with vaccines or bacterial substances so far has yielded indifferent results

Intubation and Tracheotomy

Mechanical treatment of relief of obstruction to breathing should become less and less necessary with prompt treatment with antitoxin That it is still very frequent is a reflection on the intelligence and thoroughness with which we apply the facts of preventive medicine

Choice of Operation — Intubation is indicated in all cases of diphtheria of the larynx with sufficient obstruction of breathing Tracheotomy is indicated in low obstruction of the trachea where there is a tendency to chronic stenosis where the cartilages are infected and in some cases of phlegmonous laryngitis In some cases the repeated coughing out of intubation tubes may indicate tracheotomy Ulceration or granulation in the larynx after intubation is indication for tracheotomy Under certain condition as distance from the physician or hospital tracheotomy may be preferable

Indications for Relief by Intubation or Tracheotomy — In the gradually developing stenosis of the disease the degree of obstruction that requires intubation is difficult to define Marked supra or infra sternal retraction stridor restless ness and cyanosis are late indications The presence of stridor and the use of the accessory muscles of respiration for hours without prospect of early relief is an indication fo operation If relief is postponed until the patient is fatigued by hour of hard breathing the danger of death is greatly increased Trousseau emphasized this fo tracheotomy A very considerable proportion of intubation cases urgently require immediate relief when first arriving at the hospital

Technique for Intubation — Tactile Method as Devised by O Dwyer — The horizontal position is preferable The patient is immobilized by closely and firmly wrapping or pinning a blanket or sheet about the body from shoulders to ankles binding the hands at the sides The table should not be too high about 30 inch s being satisfactory A small pillow is placed beneath the neck and upper shoulder but the head should be only slightly extended The operator stands at the right of the patient well up towards his head and the assistant who holds the gag and the patient s head is seated facing him at the head of the table Another assistant hold the patient s knees to the table The mouth should be opened enough to allow sufficient room for the examining finger but no more The gag must be held with great care to avoid its being pushed out by the patient The operator then inserts the left index finger quickly down to the larynx The more deftly this is done the better and it is well to carry the finger down as low as possible and then bring it up until the epiglottis is felt The epiglottis is raised by getting the point of the finger beneath it and held up with the shaft

tion of the patient gives greater chance of abdominal breathing Oxygen may aid In all cases of marked phrenic paralysis the Drinker or other type of respirator is essential The relief is immediate, and return of respiratory power may appear within 1 to 3 weeks Because of swallowing paralysis, it may be necessary to tip up the respirator in Trendelenberg position and to use frequent suction of the throat

In my experience diphtheritic paralysis even of the most extensive degree always disappears although it may take several months Permanent paralysis has only been seen when cerebral damage has occurred as in thrombosis

Nephritis Routine urinary examination at short intervals is desirable The diet low in protein and high in carbohydrates is of some importance

Treatment of Carriers

The need of better treatment for those cases who continue to harbor the organisms frequently is brought to urgent notice Treatment may be divided into three groups (1) germicides to attack the *C diphtheriae*, (2) treatment of the mucous membrane of the host (3) attempts to secure antibodies In the first group a very large list of germicides has been used as corrosive sublimate cresol silver nitrate citric acid acetic acid Lugol s solution tincture of iodin etc but without any benefit in my experience Churchman has urged the use of gentian violet saturated aqueous solution and this has been used repeatedly with excellent results It is practically non irritating and non toxic but its staining of everything it touches is slightly objectionable There are many cases in which it is difficult to bring the solution in touch with all the areas as the tonsillar crypts the sinuses or fossae of the nose etc and these are not benefited Efforts to remove the organisms by overriding with *Staphylococcus pyogenes aureus* or *Bacillus bulgaricus* or by the use of kaolin have given nothing but disappointment in my hands Penicillin has been used by both spray and by intramuscular injection and is highly efficient Locally applied our results have been very disappointing But on intramuscular injection practically all carriers recover in 1 to 2 weeks Occasionally *C diphtheriae* is resistant to penicillin

In the second group the most reliable results have been secured Definite clinical abnormality as diseased tonsils or tonsils with large crypts adenoids sinuses etc if associated with the organisms offers a point of attack Treatment of the abnormality if successful usually means cure of the carrier This has been especially striking on removal of foreign bodies from the nose and the removal of tonsils and adenoids In pharyngitis treatment may be directed to the disease rather than the organisms

In the third group no strikingly good results have been secured Carrier

readily detached in the trachea it will come up and close the tube or act like a valve at the end Tracheotomy instruments should therefore be ready as a precaution in neglected cases Bronchoscopes or Dr Mosher s breathing tube may often be used with great advantage in such cases In many, however if the tube is at once removed membrane may be coughed up and on reinserting the tube relief is secured Tubes of different length like the French or Bayeux short tube may give relief

Great care must be used not to traumatize the larynx with danger of persistent obstruction The tube also should be selected of a size not to press too firmly in the cartilaginous box of the larynx The ages for which the tubes are marked are averages and very often a smaller age may be used In girls smaller tubes may be used while the large big framed child may require a larger one

In adults it is often difficult to feel the larynx because of the distance and therefore intubation may be difficult

Ocular Method — By this method the tube is introduced through a laryngoscope such as Mosher s or Jackson s For this work Mosher s laryngoscope is superior because the hinge allows of opening the instrument to take tubes that will not pass Jackson s A special introducer and extractor are needed to pass through the laryngoscope The patient is immobilized as for the other method The operator sits or stands at the head of the table facing the patient while the assistant stands at the patient s right to hold and extend the head A gag may be used but is often unnecessary if advantage is taken of his opening the mouth The head is rocked back on the atlas keeping the chin forward in the sword swallowing position and held in this position This may be done over the end of the table which should be high or over a large pad on the table The laryngoscope then is introduced raising the epiglottis and exposing the larynx The tube then is inserted and released and the laryngoscope removed This method requires more instruments than the other and takes some practice but it is very satisfactory It enables the operator to see the condition of the larynx and there is less danger of trauma

Extubation is done in like manner the laryngoscope bringing the tube into view and the extractor is inserted easily

Obstruction of the bifurcation of the trachea may require relief in a small proportion of cases Here if available a bronchoscope may be used and the membrane fished out This is sometimes difficult because it is difficult to get hold of the loosened edge In many cases however large casts of the bronchi may be removed with great relief Tracheotomy may be done and the membrane then fished out with forceps or a bronchoscope may be passed through the trachea wound

Suction — The removal of obstruction by membrane in the larynx by means of suction was first practiced by Litchfield and Hardman at Willard Parker

of the finger while the end of the finger is placed just over the interarytenoid notch The shaft of the finger should be well to the right to allow room for the introducer and tube Having thus located the landmarks by touch and raised the epiglottis the tube on its introducer is introduced with the right hand and the point brought down to the opening of the larynx It is essential that the tube be in the median line The handle then is raised so that the tube is brought horizontal and in line with the larynx At the same time the end of the tube is brought over the palpating finger, hugging it closely to keep behind the epiglottis and thus present at the atrium of the larynx between the epiglottis in front and the finger behind It is then carried down into the larynx when the patient inspires and pushed off the obturator with the finger and seated properly in the larynx If properly done and relief secured the patient gives a loose whistling cough which is a very welcome sound to the operator If the patient was much tired it is wise to allow him to rest for a time on the table without further procedure Coughing is often marked and large amounts of mucus and pus may be raised The patient may be turned on his left side to facilitate this When dyspnea and dilatation of the heart have subsided the silk fastened to the tube may be removed The object of this string is to retrieve the tube in case it gets into the esophagus instead and to remove the tube, if the intubation tube is clogged at once with membrane or does not relieve In some cases the silk is left being fastened to the face with adhesive or over the ear This enables anyone whether skilled or not to remove the tube if it becomes obstructed It often disturbs the patient greatly and offers him a chance to pull out the tube so that it is required to restrain the hands In removing the string the patient is in the same position as for intubation The operator passes his left index finger down to the larynx pulls up the epiglottis and holds the end of his finger on the side of the intubation tube The silk loop being cut the string is removed by pulling straight up over the upper incisor teeth to avoid cutting the epiglottis

Extubation — The patient and operator and assistants are in the same positions as for intubation The patient's head may be somewhat farther extended but not too much as it brings the larynx against the pharyngeal wall The left index finger then is passed as before lifting up the epiglottis and locates the central protuberance of the lip of the tube at the interarytenoid notch The extractor then is carried down to the finger keeping the median line and the handle raised while the tip of the extractor is brought over the feeling finger and thus directed into the lumen of the tube It is important that the handle be brought up to a vertical position or just beyond The jaws of the extractor then are opened gripping the tube and the extractor carried straight up as far as possible then curved gradually bringing the tube out of the mouth

Operative Dangers — In doing intubation besides the technical difficulties there is a possibility that the membrane will occlude the tube or that, being

by avoiding as far as possible the known causes The phlegmonous cases are far more likely to lead to this condition than the diphtheritic and the question of doing tracheotomy has been considered already

For the many years it has been the practice at the South Department to do secondary tracheotomy in cases showing stenosis without improvement at the end of 3 weeks so as to leave the larynx free from further irritation In most of such cases the larynx has cleared to a complete or nearly complete degree by this simple means alone Dilatation of the case with cicatrix may be done after healing is present

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Hospital New York in 19 ? As done in the South Department of the Boston City Hospital a special suction tube is used which has proved of great value In only about 15 per cent of laryngeal diphtheria obstructions have we found relief by removal of membrane as the swelling was still significant in many although Litchfield and Hardman had 4? per cent success In low membranous obstruction of the trachea or bronchi the suction tube has been of the greatest value as forceps removal was very unsatisfactory

Tracheotomy — The mortality is somewhat higher in tracheotomy than in intubation although it is impossible now in this country to compare the two operations For the technique of tracheotomy the reader is referred to books on surgery

Management of the Intubation Cases — After intubation and antitoxin the patient's relief allows a needed sleep The room should be well ventilated and not too warm Intubed patients do well out of doors, even in cold weather, if they can be properly watched Because of the danger of sudden obstruction or coughing up the tube they should be constantly watched and someone should be available to give relief when needed The fluid intake should be large No harm has been found to occur from allowing intubated patients to drink sitting upright Casselberry recommended a position with the head lower than the body so the patient must drink up hill with the idea of preventing aspiration The pneumonia incidence has not been increased however by the ordinary position Northrup by special substances in the food showed post mortem that there was no aspiration of food in his cases

Duration — The tube must be kept in until the obstruction has subsided In most diphtheria cases under modern treatment this is 3 to 4 days although it may be much longer The amount of cough expectoration prostration or lassitude and fever (if other infection as pneumonia is absent) may serve to tell the course of the diphtheria While it is desirable to have the tube out as early as reasonable more harm may come from removing and reinserting the tube than from its remaining in position

Chronic Intubation Cases — Following intubation in some cases the larynx does not return to normal but continues to show complete or marked obstruction These chronic cases result from various causes Of these injury from inserting or removing the tube pressure from too large a tube secondary infection producing a phlegmonous hard swelling of the larynx with secondary ulceration and sloughing and involvement of the cartilages in the infection are the most important

With proper management the number of chronic tubed cases may be kept very low Less than 0 5 per cent of the intubation cases at the South Department have shown stenosis lasting over 3 weeks and of these there are now only 4 who have not dispensed with the tube The treatment should be prevention

CHAPTER VII

PLAGUE

By George W. McCoy

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Introduction

Plague is to be regarded as one of the vanishing diseases of mankind. In the culturally advanced parts of the world at the present time it occurs only in occasional small epidemics and one may predict confidently that there will be even fewer outbreaks in the future. The disease in man always is dependent on infection derived from members of the rodent family; consequently if these sources could be eliminated or greatly reduced there would be no plague in man. It probably is owing to measures taken against rodents that in the last half century

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its height in 1348-50, apparently had cases of both bubonic and pneumonic types. There was one noteworthy development from this outbreak in that it led to the recognition that epidemic disease was something against which precautions could be taken, especially the establishment of quarantines to prevent travelers from infected regions going to those areas still free of the disease. We may doubt that the measures taken were effective, but they represented a realization that disease was not necessarily an affliction to be dealt with by charms and incantations but that more rational measures might avail. Some ancient chronicles seem fantastic in the light of present knowledge, such as sudden deaths from plague of previously healthy people and epizootics among domestic animals. Rats are not mentioned in a way that indicate an understanding of the important relation of these animals to plague.

The second great epidemic was in the latter half of the seventeenth century and gave rise to what usually is called the great plague of London in 1665, about which Defoe[3] wrote so graphically and of which Pepys also makes mention. In Marseilles there was a fairly extensive epidemic that reached its height about 1720. While some outbreaks occurred in the interval, it was not until 1894 that the last world-wide prevalence (pandemic) of the disease began.

There are reservoirs of rodent plague in Africa, Manchuria and China from which the disease has spread periodically to better known parts of the world. According to most accounts the recent pandemic originated from one of these rodent reservoirs in the interior of China and first attracted the attention of the Western World when in 1894 it appeared in Canton and Hong Kong. This was the first epidemic since the development of modern methods of scientific medical research, and it speedily resulted in a flood of information that made the way clear for the control of plague by rational measures. The disease early spread from China to India and the Middle East. In 1899 the Hawaiian archipelago and the Eastern Coast of South America were among regions infected, and the following year the disease appeared on the western coast of the United States, first at San Francisco, a little later in Mexico and on the west coast of South America. The Gulf Coast region of the United States was first found to be infected in 1914, when the disease was recognized at New Orleans, where it persisted until 19[illegible]0 but never to an alarming extent. During this period several other Gulf Coast cities, Galveston, Beaumont and Pensacola, each had a few cases, but in none of these was the outbreak serious. For reasons that are not clear plague never has occurred on the Atlantic seaboard of the United States.

conspicuous success has attended efforts of the public health authorities in controlling the disease in man Clinically and epidemiologically plague exists in two principal types First to be mentioned and probably the primary type from which the other is derived, is the bubonic form characterized clinically by involvement of the lymph nodes and usually transmitted among rodents and to man from the rodent host through an arthropod vector, usually a rat flea The second type the pneumonic or pulmonary is characterized by symptoms of a respiratory infection presents pronounced pathological changes in the lungs and is transmitted directly from person to person by droplet infection Although when once established it is so transmitted from person to person it is probable that often the original case in the series started from a bubonic one that had developed a secondary plague pneumonia Comparatively recently the threat of plague in the United States was felt to be so important that in the summer of 1941 a special Plague Control Conference was held by the United States Public Health Service and representatives of western states to try to devise methods especially designed to prevent spread of sylvatic or rural plague to urban communities and particularly spread in areas that might be used by the armed forces At that time it was recognized that there probably would be military camp sites established in regions in which sylvatic plague could be expected

History

The history of plague has been the subject of many writings in ancient medieval and modern times In the Book of Samuel[1] there is an account of an affliction prevailing among the Philistines which some authorities regard to have been plague by reason of the association mentioned in the biblical record of mice and emerods the latter being held by some students to mean buboes Rufus of Ephesus mentions about the year 100 A D what clearly appears to have been plague He recorded the characteristic buboes and the high fatality His account deals with an outbreak in Egypt Lybia and Syria Many epidemics have been reported in comparatively recent historical times and while there may be much doubt as to the nature of some of them two important outbreaks stand out as probably valid In the fourteenth century there occurred the great epidemic known as the 'black death' which is said to have destroyed a quarter of the population of Europe and to have led to great social and economic changes This epidemic which reached

the cultures show marked variation in the microscopic appearance many atypical trypanosome like, globoid dumbbell forms and other bizarre shapes being found After 24 hours or more of growth in plain broth the culture leaves the medium clear with a slight deposit on the sides and bottom of the tube and microscopically the organism is likely to appear in streptococcus like chains a peculiarity of some value in identification Plague cultures have the property of developing more promptly and abundantly at a temperature around 30 C rather than at the usual temperatures of laboratory incubators, 37 C The plague organism exhibits about the same resistance to physical and chemical germicidal agents as other non spore forming bacteria

While the plague organism grows well on ordinary culture media the addition of serum or blood promotes growth Various selective and enriching media have been devised These are reported to be of special value for dealing with contaminated material

The plague organism is pathogenic for nearly all rodents guinea pigs rats and mice are especially useful for study purposes Rabbits are less satisfactory Most domestic animals and all birds are insusceptible Cats appear to be an exception and indeed a few human infections seem traceable to the cat Guinea pigs and rats that are inoculated with fully virulent cultures of the organism usually die on the fourth or fifth day and present well marked pathological appearances that are of great aid in identification While lesions differ somewhat in different species of laboratory animals characteristically in acute plague there are bloody or blood stained serous reactions at the site of inoculation a necrotic hemorrhagic bubo necrosis of the liver and an enlarged spleen In less acute cases there are likely to be purulent foci in the region of lymph nodes and in the lungs the latter especially in guinea pigs The reaction in animals probably is due to a toxic product liberated by the disintegration of the bacterial cells The usual methods of inoculation are successful and there is the property shared by a few bacteria of being able to penetrate the shaven skin of the experimental animal and transmit the disease in that way almost as readily as when the culture or infected material is given by a hypodermic syringe The introduction of infected or suspected material into a subcutaneous pocket also is practiced for isolating and making a diagnosis of the organism

There is one other organism occasionally found in connection with human pathology that is exceedingly similar to that of plague This is *Pasteurella pseudotuberculosis rodentium (Pfeiffer)*[2] which so closely resembles *Pasteurella pestis* that the question has been considered as to

Zentner[4] reports for the United States to the end of 1940 a total of 496 cases with 312 deaths Of these about 80 per cent were in the Pacific Coast states and the remainder in the Gulf Coast region So far as can be judged from Zentner s data, 471 would be classified as of urban or murine and 25 as of sylvatic or rural origin There have been perhaps a dozen cases, chiefly rural, since the date of Zentner's report During this pandemic of plague the British Isles were invaded at a number of places[5] Rodent and human infection occurred in London Glasgow and in other seaports where it appears to have been controlled readily

There were various ports of Continental Europe where the disease occurred during this modern prevalence but in none was there a very severe outbreak The advance of our knowledge acquired during this pandemic in addition to the pioneer work of Kitosato and Yersin, comes largely from the investigations of the Russian, Verjbitski[7], and even earlier than that although less well known, from the work of Simons[8] The work of the so called Indian Plague Commission[9], which carried on its investigations chiefly in the first decade of the present century, has been the most thorough and fruitful of any This Commission proved among other things that the disease was primarily one of rodents, especially domestic rats, and that the infection was transmitted from rat to rat and from rat to man chiefly by the rat flea, *Xenopsylla cheopis*, often spoken of as the Indian rat flea

ETIOLOGY

The organism causing plague often spoken of as the *Bacillus pestis*, but more correctly designated under the newer nomenclature as *Pasteurella pestis*, was discovered in 1894 at Hong Kong China, almost simultaneously by the French bacteriologist, Yersin, and by Kitosato, a Japanese medical research worker The organism usually is classified as a member of the hemorrhagic septicemia group of bacteria It is a gram negative short, non-motile rod readily cultivated on the usual laboratory media and having well marked cultural and pathogenic properties The organism stains well with ordinary dyes and occurs typically in tissues of animals dead of acute plague as a barrel shaped or bi polar rod, in older lesions forms resembling gram negative cocci are very characteristic On plain agar it produces when freshly isolated a tenacious sticky growth which may be drawn out in a fine thread a property which is highly suggestive for diagnosis of the organism When the agar is made with a larger than usual amount of sodium chloride, 2 or 3 per cent,

as an occasional case at long intervals sporadic or whether there is a definite excessive prevalence that justifies the use of the term 'epidemic Race age and sex apparently have no relation to the prevalence of the disease excepting as they influence the opportunity for acquiring the infection

Mode of Infection and Clinical Type

As has been indicated before when viewed with respect to mode of infection and clinical type the bubonic form of plague is spread by arthropods[11] usually fleas and the pneumonic type is spread by direct human to human transfer of infection droplet

Seasonal and Geographical Distribution

In most places plague is a disease of distinctly seasonal prevalence the ordinary bubonic type being confined largely to the period of the year when the mean temperature ranges below 80 F an epidemic speedily subsides when the temperature reaches 85 F The pneumonic type as has been said is spread mostly from person to person and prevails chiefly in cold seasons of the year Viewed with respect to the geographical distribution in a country especially in the United States we may consider that plague of cities sometimes spoken of as urban usually is due to infection from members of the rat family murine plague All species of rats may develop plague the black rat apparently playing the major role in some areas the gray rat in others Still other species of rats are important to the spread of the disease in some foreign countries

Plague derived from rural dwelling animals particularly ground squirrels prairie dogs and other members of the rodent family often is spoken of as sylvatic sometimes spelled selvatic or silvatic plague This term is used for the disease either in rodents or in man

Dealing first with the bubonic form of plague in urban areas it has been observed that infection among rats precedes that among people and that usually the outbreak is of slow onset scattered cases occurring sometimes over quite long periods before the transfer of infection from rats to man becomes sufficiently marked to attract attention The early cases in man are likely to pass unrecognized When murine plague spreads from one area to another locally it is doubtless by peripheral infection of successive groups of animals Long distance spread is usually by rats carried on vessels or other means of transportation

whether one is not a mutant of the other, particularly as there is good evidence of some cross immunity between the two An important point of difference is that this organism has the property of making litmus milk deep blue while the plague organism usually makes it slightly red, also the pseudotuberculosis organism is but little pathogenic for the white rat *Pasteurella pseudotuberculosis rodentium* very rarely produces disease in man and when it does, the clinical conditions and pathological lesions bear no resemblance to those of plague This and similar organisms may be found occasionally in stock laboratory animals and in wild rodents

The causative organism of tularemia[10] bears no resemblance to that of plague although the two produce pathological appearances in guinea pigs that often are indistinguishable on gross examination An important point here is the inability of the tularemia organism to grow on ordinary culture media

There are great dangers to laboratory workers dealing with plague, and the utmost precautions should be taken

Active immunity in animals can be produced with either dead or living cultures and Wayson and his associates recently have devised a plague vaccine of dead organisms for active immunity which in experimental animals seems to be more successful than others It has not been applied to human prophylaxis Selected strains of dead and living cultures used to immunize horses give rise to protective serums, which are useful for immunological diagnostic purposes but are of comparatively little value therapeutically In any situation in which it is important that the presence of plague be established beyond doubt, protection tests are carried out using the culture in question to determine whether its pathogenic action will be neutralized by an antiserum prepared by the immunization of animals with a thoroughly accredited culture or actively immune rats may be inoculated with the culture being studied Such tests need suitable controls of non-immune rats which, of course should die of plague while the immune animals survive

Epidemiology

The most essential feature in connection with the prevalence of plague in man is that it always is dependent directly or indirectly on the occurrence of the disease among rodents There always is an animal reservoir from which human plague is derived, whether the disease occurs

detected The exact significance of this finding is not clear but it may be related to the carrying over of the infection from year to year

There are several observed peculiarities of sylvatic plague that apply with special force to the disease in the United States First the area of rodent infection involved is enormous extending from the Pacific Coast as far east as Colorado Kansas Oklahoma Texas and the Dakotas It is not to be understood that the epizootic is uniform or continuous over this area but rather that the disease exists in pockets of animal life, ground squirrels prairie dogs and other rural rodents in large areas are infected

It has been suggested that plague in the wild rodents may have been present for a long period in the areas of infection but was not detected earlier because no investigations were made Most epidemiologists, however, are of the opinion that spread has been from one focus established on the Pacific Coast about 1900 rather than that the infection is autochthonous

The second feature and one of importance in medicine is the extremely small number of human cases that develop in the large area of rodent infection as not more than one or two cases a year are found Finally there is a suggestion that the mortality of human plague of squirrel origin is somewhat less than that of rat origin with a tendency in some cases to be subacute ending either in recovery or death

The chief danger from sylvatic plague would appear to be that it may result in transfer of infection to rats in cities where of course, much larger numbers of persons would be exposed to the risk of becoming infected than is the case in rural areas It appears likely that the outbreak of murine plague in Los Angeles in 19 4 was of sylvatic origin The tenacity with which plague remains in certain areas is well illustrated in Hawaii where rodents especially wild rats in rural regions have been infected since 1899 Dozens of species of susceptible wild animals exist in the United States and an equally large or a larger number of vectors are involved in the ecological problem of the prevalence of sylvatic plague In Siberia and Manchuria several species of rodents are known to be infected[14] One the tarabagan *Arctomys bobac* a member of the marmot family is regarded as especially important This rodent is much sought for on account of its pelt which is an important article of commerce The tarabagan is considered to be the most likely source of the epidemics of the pneumonic type that have prevailed in Manchuria and neighboring areas The danger of human infection from these rodents seems to be at least in part from skinning the animals In South

Arthropod Vector

With the rare exception of infection by the bite of a rodent the bubonic type of plague urban or rural is transmitted always from infected rodents to man by the bite of fleas very frequently a special flea known as the Indian rat flea *Xenopsylla cheopis* This flea bites man readily It has been suggested that the human flea *Pulex irritans*, may serve to convey the infection from person to person but the evidence is not conclusive

It appears from the careful studies of Martin and his associates[11] that while many fleas feeding on an infected rat take up plague organisms only a few become effective vectors for transmitting the disease to other rodents or to man depending somewhat on the degree of septicemia in the infecting host and subsequent environmental conditions In the stomach of these effective vectors the plague organisms multiply somewhat as in a culture tube until they obstruct the part of the alimentary tract known as the proventriculus which may require as long as two or three weeks When this obstruction occurs the flea encounters difficulty in getting another blood meal and in endeavoring to do so is likely to regurgitate a culture of the plague organism into the wound made by the piercing organs This so called "blocked flea" remains infective during its life but this often is shortened by the very existence of the blocking Flea transmission experiments are more successful at temperatures 73 to 78 F than at 82° to 85° F Bedbugs, lice, ticks and other arthropods have been suggested as carriers in nature, but there is no good evidence to support the view with respect to any of these

Sylvatic Type—In the sylvatic epidemiological type of bubonic plague the microorganism is indistinguishable from that found in other types and the same mechanism of transmission prevails as in the urban type[1], but here of course some rural living rodent is the source of the infection, and the arthropod vector involved is that usually associated with the rodent In the sylvatic type it is probable that peripheral geographical spread occurs but judging by the long distance sometimes intervening between infected areas, it has been suggested that some living agents such as birds may serve to transfer the disease by carrying infected rodents or their carcasses or their parasites

In studies of sylvatic plague in ground squirrels in California, Meyer and associates[2] reported latent plague which represents a stage of survival in the tissues of wild rodents in which rodents no lesions were

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regions where the epizootic has prevailed for a long time It is possible that hereditary transfer of resistance may occur

In recent times plague appears not to have been important in armies but in 1798 99 Napoleon s army in Egypt and Syria is reported to have suffered very extensively from it[15]

Pathology

Gross pathological appearances in the individual dead of plague vary with the type In the bubonic form there may be subcutaneous and subserous hemorrhages varying from petechiae to large effusions of blood These, of course, are not peculiar to plague It appears that occasionally a local lesion may mark the site of entrance of the infecting organisms The characteristic lesions are in the initially involved lymph nodes When the incision is made over such a structure, one finds blood stained serous fluid in the subcutaneous tissues and sometimes distinct hemorrhages surrounding the node The lymph nodes are enormously enlarged and broken down into a putty like blood stained mass Nodes lying in the direction of lymph flow show the same changes but usually less advanced The whole appearance of the primary bubo is so characteristic that no difficulty is encountered in making a diagnosis by one who is familiar with the gross pathological appearances The spleen is much enlarged and very dark in color The liver may show signs of fatty degeneration In one case fatal on the sixteenth day plague abscesses were found in the regional lymph nodes lungs liver and kidneys In the pneumonic type the appearance is that of a lobular or a lobar pneumonia and is not characteristic as is true in the bubonic form

As in man acute plague presents rather characteristic lesions in naturally infected rats subcutaneous injection bubo enlarged dark spleen granular liver and pleural effusion For practical purposes these lesions are diagnostic although for any important decision bacteriological confirmation is necessary A subacute or chronic form of plague is found in rats with lesions much less characteristic than in the acute form chiefly abscesses in lymph structures and viscera

Symptoms

The incubation period may be as much as 10 days but usually is 4 to 6, a day or two less in the pneumonic type In cases of squirrel origin

Africa and South America, other important areas of sylvatic plague infection various species of rodents are involved. In man the main types, bubonic and pneumonic, may run as nearly pure epidemics of one or the other more often the bubonic but with a few cases of the other type intermingled. Within comparatively recent years it has been recognized especially in Egypt and other parts of Africa, that epidemics may be made up of large numbers of cases of both types.

Pneumonic Type.—This clinical and epidemiological form is spread usually directly from person to person, probably by droplet transfer. The outbreak may be inaugurated by direct contamination of the upper air passages of man from contact with an infected rodent possibly through removing the pelt, subsequent transfers being directly from person to person. Another mode of origin of the epidemic may be from a bubonic case which has developed a secondary plague pneumonia as a complication from which other persons are infected and a series of human to human transfers so inaugurated. This type is known largely from great epidemics in Manchuria, one in 1910-1911 with a mortality of about 60 000 and the other in 1917-1921 with a mortality of 10 000 to 15 000.

The pneumonic form may be spread from place to place by humans in the incubation period or the early clinical stages of the disease but usually develops in connection with bubonic cases. Two small outbreaks of the pneumonic type have occurred in the United States of America, one in 1919 at Oakland, California with 13 cases and 13 deaths and one in 19 4 at Los Angeles, Cal with about 33 cases and 31 deaths. In each of these urban epidemics the primary source probably was sylvatic plague among ground squirrels.

The question as to how plague naturally terminates among rodents and therefore among people can not be answered definitely. Temporarily the epidemic may be much diminished by elevated atmospheric temperatures which tend to bring infections to an end probably by reducing the effectiveness of flea transmission. A factor of long range importance is the increased immunity of rats and other rodents. It has been shown that after plague has been present in a community for a considerable period of time a large proportion of the rats become immune. Doubtless when this fraction of the rat population has grown high enough to break the chain of transfer the infection automatically comes to an end. The same factor doubtless exists with respect to the rodents involved in sylvatic prevalence of the disease indeed immunity is known to develop among the ground squirrels of North America in

regions where the epizootic has prevailed for a long time It is possible that hereditary transfer of resistance may occur

In recent times plague appears not to have been important in armies but in 1798 99 Napoleon s army in Egypt and Syria s reported to have suffered very extensively from it[13]

Pathology

Gross pathological appearances in the individual dead of plague vary with the type In the bubonic form there may be subcutaneous and subserous hemorrhages varying from petechiae to large effusions of blood These of course are not peculiar to plague It appears that occasionally a local lesion may mark the site of entrance of the infecting organisms The characteristic lesions are in the initially involved lymph nodes When the incision is made over such a structure one finds blood stained, serous fluid in the subcutaneous tissues and sometimes distinct hemorrhages surrounding the node The lymph nodes are enormously enlarged and broken down into a putty like blood s ained mass Nodes lying in the direction of lymph flow show the same changes but usually less advanced The whole appearance of the primary bubo is so characteristic that no difficulty is encountered in making a diagnosis by one who is familiar with the gross pathological appearances The spleen is much enlarged and very dark in color The liver may show signs of fatty degeneration In one case fatal on the sixteenth day plague abscesses were found in the regional lymph nodes lungs liver and kidneys In the pneumonic type the appearance is that of a lobular or a lobar pneumonia and is not characteristic as is true in the bubonic form

As in man acute plague presents rather characteristic lesions in naturally infected rats subcutaneous injection bubo enlarged dark spleen granular liver and pleural effusion For practical purposes these lesions are diagnostic although for any important decision bacteriological confirmation is necessary A subacute or chronic form of plague is found in rats with lesions much less characteristic than in the acute form chiefly abscesses in lymph structures and viscera

Symptoms

The incubation period may be as much as 10 days but usually is 4 to 6 a day or two less in the pneumonic type In cases of squirrel origin

where the incubation period often is easily determined by reason of the history of squirrel contact, it has been noted to be about 5 days in several instances

Bubonic Type

The onset of plague usually is rather sudden with a chill or chilliness fever, headache, sometimes vomiting and other indications of the onset of a severe infection, the skin is hot and dry Some observers have laid great stress on the appearance of anxiety and the injected conjunctivae, but the first clinical manifestation distinctly to suggest plague is pain and swelling in the region of what is to become the primary bubo In cases of murine origin about two-thirds of the initially involved lymph nodes are in the inguinal region, chiefly femoral the remainder mostly axillary and cervical and with a few in other locations as precubital and popliteal In some cases the primary buboes are multiple In the United States, in plague of sylvatic origin, the initial involvement is oftenest in the axillary region The bubo develops very rapidly into a distinct tumor with pronounced surrounding edema The fever continues sometimes with a drop on about the third day, for about a week in cases that are likely to recover when defervescence begins If the fever remains high the outlook is distinctly poor Nervous systemic manifestations range from mental confusion to wild delirium and coma In addition to such symptoms probably toxic in nature, definite meningeal involvement is encountered in a few cases as a complication[16] of the bubonic type, and very rarely primary plague meningitis has been observed Clinically the condition is said to resemble cerebrospinal or other acute meningitides headache stiff neck positive Kernig's sign The plague organism is to be found in the cerebrospinal fluid and the cases are fatal Pneumonia may develop as a complication, which is manifest by bloody sputum dyspnea and cyanosis and nearly always proves fatal The chief importance of this complication however is that such cases may be the source, from which the pneumonic form of the disease is acquired and indeed probably may serve as the starting point for an outbreak of the pneumonic type If recovery is to take place in the bubonic form temperature drops general symptoms become ameliorated the bubo subsides or breaks down and the patient goes into convalescence A few cases take a rather subacute course and there may be suppuration of the primary bubo One such was as follows[17] A 13 year old boy 5 days prior to the onset of the disease had been successful in squirrel hunting

illness began with headache and vomiting the temperature was 104 F in the first 48 hours The left axillary lymph nodes were enlarged and tender Fever continued and 5 days from onset all superficial lymph nodes were enlarged and tender On the tenth day a pustular eruption occurred which was generally distributed over the body The sputum was slightly blood tinged for a few days His condition deteriorated rapidly, and death ensued on the sixteenth day

Pneumonic Type

The pneumonic type usually has a stormy onset with chill fever, often pain in the chest and in about 4 hours blood stained sputum These cases go on to a rapidly fatal termination in the great majority of instances Perhaps as good a description as any is the following from Dr Wu Lien Teh[11]

After an incubation period of 2 to 6 but commonly 3 days the *patient feels drowsy and dizzy with headache and lack of appetite He* complains of a chilly feeling and develops a moderate temperature of 10 -3 F and a fast soft pulse This condition usually lasts for 24 hours before cough sets in at first dry but quickly accompanied by liquid frothy sputum tinged with bright red blood In a fair percentage of cases the hemorrhage is considerable the floor and bedding being profusely covered with blood while occasionally the patients die without experiencing any cough or hemoptysis The period intervening between the appearance of the fever and the first sign of cough is most important for those in charge of contacts because this is the non infective interval when the sick may be removed without endangering the others As soon as cough appears the danger of infection becomes greater'

Anginose and Tonsillar Forms

Anginose and tonsillar forms have been described cases in which the primary local manifestations are in the throat and in the lymph nodes *of the neck*

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Septicemic Type

Blood stream infection in plague occurs under two conditions, (a) any case is likely to develop septicemia at some time during the febrile course, this occurs often even in patients who go on to recovery, (b) a few cases are seen in any extensive epidemic in which there is a heavy septicemia fom the outset without a primary bubo infection probably having been introduced directly into the blood stream These have a very stormy onset and an acute course often with marked hemorrhagic manifestations, and are said to be almost uniformly fatal

Diagnosis

Clinical diagnosis of either the bubonic or pneumonic form in the presence of an epidemic is easy Isolated cases are likely often to be missed because the physician is not thinking of this disease In the bubonic type the rather sudden onset of the usual symptoms of a severe acute infection is suggestive but these manifestations are common to many acute infectious diseases It is only with the appearance of the bubo that one s attention is likely to be directed to the possibility of plague The first indication of the bubo is pain and tenderness in the region of one of the peripheral lymph nodes oftenest in the groin especially in the femoral area Within about 24 hours in addition to the subjective local symptoms a swelling is to be detected that increases for several days and is not well circumscribed but rather diffuse giving the impression of a gradually sloping elevation rather than of an abrupt rise

In order to confirm the clinical diagnosis it is necessary to isolate the causative organism by laboratory methods The most convenient pro-

cedure although a somewhat painful one is to aspirate material from the swollen node A hypodermic syringe containing about 0 5 c c of physiological saline or nutrient broth is used The needle is inserted into the interior of the swelling the contents of the syringe forced into the mass and the plunger withdrawn The injection and suction may be done several times without removing the needle A few drops of blood stained fluid will be secured from which smears may be made immediately and the bubo contents inoculated on ordinary laboratory media Blood smears and cultures are made in the ordinary way If the smears from bubo juice or from blood show characteristic bacilli the diagnosis is strongly supported since no other disease of man gives a similar microscopic appearance in material taken during life from a lymph node or from blood In 24 hours the cultures will show characteristic growth and a few simple laboratory tests serve to establish the diagnosis In important cases it is advisable to inoculate rats and guinea pigs also, these will present characteristic pathological appearances at postmortem and the organisms may be recovered by appropriate methods In exceptionally important situations as the first case in a locality not before infected it is also advisable to inoculate two series of experimental animals with the suspected culture protecting one series with antiplague serum, the other series serving as a control

In the pneumonic form of the disease the sudden onset bloody not rusty sputum and the prevalence of other cases in the vicinity should give a clue Smears and cultures may be made directly from the bloody sputum but positive results are obtained more readily by inoculating animals with the sputum, and from these animals pure cultures are secured easily

In either type blood cultures are likely to be positive, but as the organisms are more scanty than in the bubo juice or in the sputum the chances of successful cultures are diminished Serological tests have been employed but are of more value in establishing a diagnosis in persons in process of recovery or who have recovered than in acute conditions Agglutination and complement fixation tests have been used but generally they become positive too late to be of much help to the practitioner

Differential Diagnosis

Not many diseases are likely to cause confusion with typical cases Tularemia usually mentioned in connection with differential diagnosis

the symptoms are so mild that the patient does not find it necessary to go to bed The bubo and a little fever are about the only manifestations A few cases of this nature are said to develop in any extensive epidemic probably being due to the better resistance of the individual In other outbreaks this type forms a large percentage of the cases this fact being accounted for probably by the lesser virulence of the infecting strain Macchiavello[18] reports an attenuated form of plague under the name of ingua de frio, cold inguinal bubo' The diagnosis of pestis minor is made by cultivation of *Pasteurella pestis* from the infected lymph node

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cases the death rate has been about 60 per cent In the outbreak in the Gulf Coast States the death rate was approximately 40 per cent Death usually occurs about the end of the first week The pregnant are said usually to abort The epidemic in Dakar (Africa) in 1944 numbered 567 cases with a 91 per cent death rate A few cases become somewhat chronic and death may be delayed for a month or even longer The bubonic type of squirrel origin in the area of sylvatic plague in the United States has had a death rate of approximately 50 per cent and there is a tendency to chronicity One of these cases perished on the sixteenth day with findings at the autopsy of multiple foci of purulent material in the lymph nodes and viscera Death usually occurs from 5 to 7 days after onset In future outbreaks chemotherapeutic agents may reduce the death rate

The pneumonic type of plague offers an almost uniformly unfavorable prognosis and death occurs usually within 3 or 4 days of onset A few recoveries have been reported but some of these are looked on with some suspicion that is the question arises as to whether they were truly examples of the pneumonic type of the disease One case of recovery from pneumonic plague has been reported in an individual infected in the laboratory who had been immunized ' with vaccine

Septicemic Type—Some authorities recognize a primary septicemic type of plague in which there are no buboes but infection is manifested by an overwhelming septicemia that is practically invariably fatal It is to be understood of course that either bubonic or pneumonic type if at all severe results in septicemia, readily established by positive blood cultures The development of pneumonia or of meningitis is almost always a precursor of death

In pestis minor the prognosis is good

TREATMENT

The general treatment of plague does not differ from that of other serious infectious diseases for which there is no specific remedy Bed rest nursing diet sedatives if necessary attention to the circulation all need the same consideration as in other serious conditions The local treatment of the bubo formerly was thought to be important but the concensus now is that aside from opening surgically a *definitely fluctuating* node the local lesion may be ignored Experience with excision and with the injection of antiseptics have given results that do not warrant repetition of the procedures

of the bubonic type, should give no trouble clinically because of the usually less pronounced symptoms the initial ulcerative lesion at the site of entrance of infection, the different type of bubo and the low mortality The laboratory examination speedily would clear up any question, since an agglutination test would be positive for tularemia after about 10 days, and the successful cultivation of the plague organism would identify that disease immediately

Gonorrheal and chancroidal buboes often have given rise to difficulty and the writer has had to watch cases in which this question was involved for several days until the diagnosis became clear In the venereal infection the bubo is likely to be higher in the groin, that is above Poupart s ligament, while in plague it is likely to be below the ligament in the femoral region The venereal bubo has a more pronounced elevation and of course laboratory tests give different results The general symptoms in plague usually are much more pronounced than those in the venereal infection Epidemic typhus was long confused with plague but should not cause trouble, the prevailing type of epidemic and development of the bubo in one and of the rash in the other should aid in a clinical diagnosis which could be definitely established by laboratory tests in either disease

The condition known commonly as climatic bubo more properly designated as lymphopathia venereum has caused confusion but it seems difficult to understand how this occurs since plague is a very acute rapidly progressing disease while lymphopathia venereum progresses slowly usually without the pronounced constitutional symptoms observed in plague Filariasis also is said to be capable of causing difficulty but one hardly sees how this is likely and the same consideration would apply as in climatic bubo As in many other situations especially in the study of epidemics one must be guided in making a diagnosis by attending circumstances especially the type of disease prevailing rather than on clinical manifestations in any one case in other words, the epidemic must be recognized rather than any single case

Prognosis

Prognosis varies In large epidemics of the bubonic type usually the death rate is high In India and China it often approaches 90 per cent a little lower figure would hold for some outbreaks that have occurred on the Western Coast of the United States where excluding pneumonic

cases the death rate has been about 60 per cent In the outbreak in the Gulf Coast States the death rate was approximately 40 per cent Death usually occurs about the end of the first week The pregnant are said usually to abort The epidemic in Dakar (Africa) in 1944 numbered 567 cases with a 91 per cent death rate A few cases become somewhat chronic and death may be delayed for a month or even longer The bubonic type of squirrel origin in the area of sylvatic plague in the United States has had a death rate of approximately 50 per cent and there is a tendency to chronicity One of these cases perished on the sixteenth day with findings at the autopsy of multiple foci of purulent material in the lymph nodes and viscera Death usually occurs from 5 to 7 days after onset In future outbreaks chemotherapeutic agents may reduce the death rate

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Treatment

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Various serums produced by the immunization of horses with antigens prepared in different ways formerly were much in vogue in treatment. However, in recent years they have been discarded to a great extent for what seems to be more promising therapeutic agents. It has been suggested that antiserums made by immunizing animals with the locally prevailing strain would give better results. Bacteriophage has been used, but the results are not encouraging. Recently members of the sulfonamide group, especially sulfadiazine and sulfathiazole have been used in well controlled experiments on laboratory animals, and these appear to indicate that they may be of great value in man, and a few favorable clinical reports have been made. The drugs are used as in any other severe infection and must be given early to be very effective.

Maclay-Dick[19] reports 26 cases treated with sulfapyridine with 5 deaths, 19.2 per cent. Some of the cases also were given serum. This observer reported that 30 to 45 grams of the drug were given to each case and serum in doses of 10 c c intravenously and 20 c c intramuscularly to a total of 155 c c. Suppuration of the buboes occurred in 8 or 33 per cent. Very interesting was the report that the buboes became negative for *Pasteurella pestis* 24 hours after the administration of sulfapyridine was begun.

A very recent report[20] on chemotherapy in the bubonic type of plague that of Huang and Chu indicates that sulfadiazine gives very satisfactory results. In this series prior to the use of the special chemotherapeutic agents the death rate in the epidemic was above 50 per cent. They treated 25 patients with only 5 deaths. Great emphasis is laid on the early inauguration of treatment as no case died if treated before the third day from onset, also the favorable results are indicated by the more rapid fall of temperature in the cases coming under treatment early. Usually the bubo becomes smaller, softer and less tender in response to the treatment. The first dose of either sulfadiazine or sulfathiozole was 4 grams for an adult, thereafter 1 gram every 4 hours, the drug being continued until temperature had been normal 2 days or longer. Clearing of the blood stream of *Pasteurella pestis* occurred with the clinical improvement but the organism remained viable in the buboes for longer periods and the authors suggest that this may lead to relapse.

The antibiotics penicillin and streptomycin have not been employed enough clinically to justify a final opinion as to their value, but streptomycin in experimental animals seems to be promising. The few clinical reports to date (1948) in which the latter have been used are very encouraging, more favorable perhaps than those for any other drug.

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Great care should be used in permitting exertion especially after the fall of temperature as sudden death has resulted after slight exertion during early convalescence

The pneumonic and primary septicemic types are treated symptomatically but it has been the experience that therapeutic measures are of practically no value although of course the agents mentioned above may be employed One case of laboratory infection of the pneumonic type in a scientist previously immunized with plague vaccine was treated with sulfadiazine with recovery

Preventive Measures

Personal Prophylaxis —The certain means of avoiding plague infection is to remain away from districts in which the disease is prevailing and the avoidance of suspected localities and structures Early in the latest pandemic Haffkine a bacteriologist working in India produced a killed bacterial vaccine which is reported to have been used very successfully in British India but these results have not been duplicated elsewhere

Wayson[21] devised a killed vaccine which was superior to commercial vaccines the outstanding features of which were that it was grown at 39° C precipitated by alum or alcohol after phenol killing This appears to be the most promising of the dead vaccines

Otten[2, 23] a Dutch investigator working in Java has produced a live vaccine made from selected avirulent highly antigenic cultures that appears to have given more satisfactory results in the way of protection than any other biological preparation He used this to immunize approximately two million people in the Dutch East Indies in one year and apparently his vaccine reduced the mortality by about 80 per cent Immunity in experimental animals is induced more readily by live vaccines than by killed cultures A careful appraisal of the evidence fails to convince one that an epidemic ever has been materially affected by any biological preparation excepting possibly in Otten s experience Obviously the local conditions that would require consideration of the use of vaccines vary greatly for example with the low incidence of plague in culturally advanced parts of the world an attempt to control it by vaccination would hardly be warranted On the other hand if a high incidence were anticipated it might be wise to use general vaccination perhaps with special emphasis on sanitary personnel and then it would seem desirable to use the live culture of Otten

Vaccines, apparently, are of no value in preventing the pneumonic type but they may serve to mitigate the severity Passive immunity induced by the injection of an antiplague serum may be useful in a few exceptional situations, as when an accidental laboratory exposure has occurred or another situation involving great risk develops, then a dose of this serum may offer some protection, but evidence on this point is very scanty

In pneumonic plague strict isolation of patients must be required, and all of the usual precautions that are taken for the control of spread of contagious diseases of the respiratory tract should be observed In the prevention of the spread of the pneumonic type it is reported to be of advantage to isolate all contacts as well as all patients In dealing with pneumonic plague masks and goggles are advised for the attendants or even a hood with glass or isinglass set in so that vision will be relatively unimpaired This type is highly contagious and has been the cause of many fatalities among doctors nurses and other medical attendants

Community Preventive Measures—In the light of our knowledge of control methods the public fear, even hysteria, and the disturbance of economic life, that have attended the appearance of plague in the past, should not be seen again, if this disease appears in communities having satisfactory public health conditions Urban plague requires the adoption of measures for its suppression based on the well known fact that the source of this infection is the rat The human victim of the bubonic type is not a source of danger to others, unless he develops a secondary plague pneumonia which then may spread by droplet transmission Rat populations may be reduced very greatly by poisoning, trapping and possibly even more important, by taking measures that deprive rats of food, hence garbage collection and disposal are prime factors As a long range program ratproofing especially of slaughter houses, food depots stables and other places of special rat prevalence, may be expected to give results that justify the great expense of this form of prophylaxis Rat viruses have been much employed but are of doubtful value in antiplague work no matter how useful they may be for food and crop protection It is customary to establish a laboratory to examine rats with a view to determining the geographical extent and the intensity of the infection among rodents This may be done by dissection of rodents and in recent years examination of ectoparasites from rodents and rodent nests has appeared very useful

Among rat poisons phosphorus and arsenic have long been used Recently a war developed rodenticide sodium flouroacetate (1080),

has been said to give better results than anything else It is so toxic however, that it is not safe to put it in the hand of the householder, and its use is restricted to distribution by health organizations Very recently an insecticidal agent dichloro-diphenyl trichloro ethane (DDT) has been used in conjunction with the rodenticide with a view to killing the fleas as well as the rodents The reports appear to be very encouraging Rat control is important also in the prevention of endemic typhus and Weil's disease as well as to diminish the destruction occasioned by rats eradication is not possible but the number can be greatly reduced

Rural sylvatic plague results in very few cases in persons scattered over enormous regions The areas involved are usually so extensive as to make efforts at the destruction of the wild rodents impracticable but they may be controlled or reduced in number by creating rodent free zones around urban communities designed to prevent the infection of domestic rats With the bringing of the land under cultivation automatically the problem is solved since agriculture and rodent pests do not do well together In infected rural areas where protection against plague would be exceptionally important as for a military camp poisoning by cyanide gas or using carbon disulphide to gas the burrows or toxic agents on bait such as poisoned grain probably will reduce the potentially dangerous rodent population to such an extent as to make the area safe Plague control usually is conducted by special staffs in health departments Maritime quarantine measures are intended to prevent transport of rats by ships rat proofing of ships poisoning trapping and requiring vessels to be fumigated before docking are the main procedures used

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CHAPTER VIII

GLANDERS

By CALDERON HOWE

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Synonyms – Glanders, farcy, equinia (English); Rotzkrankheit, Wurm, Farcimen (German); morve, farcin (French); morva, farcino (Italian); muermo (Spanish).

Definition – Glanders is a specific infectious and contagious disease of man and animals caused by the microorganism *Malleomyces mallei* (variously called *Bacillus mallei*, *Bacterium mallei*, *Pfeifferella mallei*).[1] Although primarily a disease of the *Equidae*, it may occur sporadically in humans as a result of contact with diseased animals or discharges from active human or animal cases and as the result of accidental exposure in the laboratory.

been used extensively in human cases The agglutination test for glanders introduced in Germany by Schnurer[9] was widely applied by Schutz and Miessner[11] and extensively assayed in the United States by Moore[12] The injection of mallein originally described by Babes in 1890[13], who called it morvine was first applied to human diagnosis by Bonome[14] The use of the precipitin reaction was first reliably reported by Pfeiler[15] and independently by Miessner[16] using mallein or similar products

Incidence

The decline in the incidence of glanders has resulted chiefly from the stringent control measures introduced by many national governments early in the twentieth century to eradicate the disease by the destruction of glandered animals Such measures have been based on the use of the mallein sensitivity tests and serum complement fixation test as means of diagnosis However the gradual disappearance of large numbers of horses from the urban scene has served also to reduce the incidence of human infection to the vanishing point

Von Brunn[17] was able to find that a total of 403 cases of glanders in various forms had been reported in the literature up to 1919 but he regarded this figure probably correctly as much less than the true incidence During World War I Luhrs[18] reported about 50 human cases in the Germany army and 58 000 horses were destroyed in the French Army 150 000 in the Germany Army because of glanders Despite this temporary increase in the mid twentieth century glanders is virtually unknown in the United States and the United Kingdom About 30 case reports have appeared in the world literature since 19 0 and only two deaths resulting from glanders both in 1937 were reported to the United States Public Health Service during the decade 1937 1947 As in the past laboratory workers handling *M mallei* are still the occasional victims of accidental infection[19]

Etiology[21 2 4]

Morphology — *Malleomyces mallei* is a short gram negative non acid fast bacillus measuring 1 5 to 3 0 micra in length 0 3 to 0 6 micra in width straight or slightly curved in shape with rounded ends and irregu

History

Glanders in its various forms is one of the oldest known infectious diseases and has been introduced and spread in every country in the world by war and trade. It was described first as a contagion by Aristotle (circa 330 A.D.) who called it *melis* (μηλις). Apsyrtos (circa 375 A.D.), a veterinarian in the army of Constantine the Great, recommended the segregation of diseased animals. Vegetius Renatus (circa 400 A.D.) adapted the Greek to Latin, calling the disease *malleus*, *malleus humidus*, *morbus humidus*, *farciminum* or *malleus farciminosus*, thereby furnishing the etymological basis for modern terminology.

Although many theories as to the nature of the glanderous disease were advanced from time to time, by the end of the eighteenth century it seems to have been accepted as infectious and its commonest forms, glanders and farcy, originally thought to be distinct, were shown to have a common etiology. Lorin was the first to record a human case unequivocally contracted by exposure to diseased horses. Rayer[3], whose monograph still stands as a milestone in the literature, collected a large series of human cases in which the disease had been clearly the result of exposure to glandered horses; he actually infected a horse with pus from one of his patients. In 1840 a series of experiments at the Veterinary School of Alfort, France, conducted by Renault and Bouley, established firmly the contagiousness of the disease for horses. Of interest is the fact that the latter investigator contracted glanders from which he suffered intermittently for forty years.

The etiological agent of glanders, *M. mallei*, although described in lesions in 1881 by Babes[4], was first isolated in pure culture in 188[illegible] by Loeffler and Schutz in Germany[5] and by Bouchard, Capitan and Charrin in France[6]. Loeffler was the first to fulfill Koch's postulates for the disease[7]. The largest part of the investigative work on the subject of glanders was reported in the literature during the fifty years following the discovery of its cause. Except for a few more recent contributions, our knowledge today of the disease and indeed its virtual eradication is directly referable to the accomplishments of European scientists, veterinarians and clinicians during that half century.

Strauss[8] was the first to demonstrate the typical and diagnostic reaction in the guinea pig testis following intraperitoneal injection of the glanders organism either in culture or in infected pus and discharges. The complement fixation test was used originally in the diagnosis of animal glanders by Schutz and Schubert in 1909[9] and since then has

Mallein.—Mallein is the name applied to the sterilized filtrate of liquid cultures of *M. mallei*, containing in solution the products of bacterial metabolism and lysis. It thus represents essentially the endotoxin of the glanders bacillus. The forms of mallein widely employed for diagnostic use have been the concentrated liquid mallein and the powdered form.[30, 8] Various methods of potency standardization have been used, none of them entirely satisfactory.[1, 3, 40, 41] Mallein is currently produced under standardized conditions at the United States Army Medical Center and the Bureau of Animal Industry, United States Department of Agriculture, Washington, D. C.

THE PATHOLOGICAL PROCESS

The tissue reaction in glanders is essentially one of focal necrosis, exudation and reparative endothelial and connective tissue proliferation. It is due fundamentally to the endotoxins of *M. mallei*.

Having gained access to the lymphatics or small blood vessels at the site of primary inoculation, the glanders bacilli lodge in various parts of these channels causing at first exudation and endothelial proliferation and then subintimal and medial degeneration. *In general* it can be said that a highly virulent strain of *M. mallei* produces vascular changes of an acute inflammatory type, while a strain of lower virulence produces proliferative changes to which the degenerative changes are secondary. Thrombosis and the formation and dissemination of septic emboli follow, causing the establishment of metastatic foci which represent the true glanders nodules or the "Rotzknötchen" first described by Virchow in 1854.

The bacillus of glanders may be so modified in virulence as to produce focal lesions differing widely in their histological textures. A highly virulent strain causes primary liquefactive necrosis and disintegration of tissue, followed by the invasion of the injured area by polymorphonuclear leukocytes. These leukocytes may also undergo liquefactive necrosis, chromatotaxis, leaving deeply staining nuclear fragments to form the core of the lesion. The strain of moderate virulence gives rise to a focal lesion of an acute inflammatory nature in which the polymorphonuclear leukocytes at the center of the lesion show little evidence of necrosis or disintegration. Strains of low virulence produce primary tissue proliferation with the formation of epithelioid and giant cells analogous to the miliary tubercle.

fairly parallel or wavy sides So called filamentous forms, usually seen in older cultures, are actually strings of bacilli which have to a certain extent lost their morphological individuality With the ordinary bacterial stains the bacilli have an irregularly granular or beady appearance, and sometimes show bipolar staining Fat bodies have been demonstrated by special stains[3] and a complex lipoidal substance has been extracted from the organism[4] A relatively non-specific nucleo protein substance similar to mallein and a soluble specific polysaccharide have been isolated from culture filtrates of *M mallei* The latter fraction fixes complement with serum from infected animals With electron microphotography the bacterial cells appear to have a definite cell membrane and to contain scattered clear refractile bodies resembling lipoid globules and opaque protoplasmic accumulations[6] The organism is non motile, is not encapsulated and does not form spores

The glanders bacillus is closely related antigenically and morphologically to *M pseudomallei* the bacillus of Whitmore which causes melioidosis (see next chapter Chapt VIII A) a glanders-like disease occurring naturally in rodents and occasionally transmitted to man[illegible] Strain variation has been demonstrated serologically and morphologically for the glanders bacillus[7]

Persistence — *M mallei* is a relatively delicate bacterium being unable to survive in dried pus or discharge for longer than a few days and in ordinary culture media not much more than six weeks It is killed by 24 hours exposure to sunlight as well as by 10 minutes' exposure to moist heat at 55 degrees centigrade However it will survive in tap water under laboratory conditions for at least 4 weeks[6] Rapid freezing and drying under vacuum (lyophilization) preserves its viability for at least 5 months[30] and its virulence for guinea pigs for at least 8 months[31]

Cultivation — Growth of *M mallei* occurs aerobically to appreciable extent on all the usual bacteriological media incubated at 37 C and is enhanced by the addition of glycerol The most characteristic growth occurs on potato infusion agar or actual slices of potato sterilized in water appearing after 48 hours as a honey like or brownish deposit and within 4 to 7 days forming the typical chocolate colored colonies with bluish green margins and diffusion of brown pigment into the medium[1] These features are not dissimilar to the growth of *Pseudomonas aeruginosa* (*Pseudomonas* or *Bacillus pyocyaneus*) Indeed there has been inconclusive evidence suggesting that these two organisms might be related antigenically[3, 33, 1]

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The gross appearance post mortem in experimental animal glanders as well as in some human cases also suggests miliary tuberculosis with many fine nodules apparent particularly in the lungs spleen and liver In other cases the glanders lesions may vary between the extremes of an abscess and an apparently solid tumor A recent lesion of small size such as might be found in the lung shows a central opaque area of necrosis surrounded by a translucent gelatinous zone outside of which is a hyperemic area In acute cases there may be also confluent organizing pneumonia with alveolar exudate consisting largely of mononuclear cells as in caseous pneumonia In older lesions the center usually is dry and cheesy and in place of the surrounding hyperemia there is an area of fibrous tissue Calcareous degeneration is much rarer than in tuberculosis

It is thus apparent that whether exudative or proliferative, the secondary glanders lesion is essentially focal in character and that there is wide variation in the degree to which individual lesions are either exudative or proliferative depending on the invasiveness of the strain the resistance of the host and the duration of the disease process It has been the common experience that strains of *M mallei* isolated from fatal human cases are more uniformly of a higher degree of virulence for guinea pigs than are strains from animals sources[70]

Glanders in Animals[4]

Horses mules and donkeys are the only animals found to harbor the infection naturally although other species may occasionally contract glanders through contact with other infected equidae All domestic animals are easily infected experimentally except cattle pigs and rats these three species as well as fowl appear to have a high degree of natural resistance Guinea pigs and hamsters are the laboratory animals most uniformly susceptible to experimental infection It is to be noted however that strains of *M mallei* from different animal sources vary in virulence which in turn may be a reflection of both individual strain invasiveness and natural resistance even in animals of generally susceptible species

Glanders in Horses — The disease in horses may be acute but usually is chronic Two types are generally recognized namely 'glanders' characterized by ulceration of and discharge from the nasal passages trachea and bronchi with involvement of the regional lymph glands and

'farcy' consisting of characteristic skin lesions or farcy buds with centripetal suppurative lymphangitis and lymphadenitis There may be any variation of either or both of these types The lesion common to all cases however is the glanders nodule always found in the lungs and pleura at autopsy[4] Grossly these nodules usually are pea sized to walnut sized with a necrotic white center a red and engorged periphery occasionally fibrous encapsulation and infrequently calcification Microscopically they present a uniform and characteristic picture not unlike the miliary tubercle The center of the nodules is composed of massed polymorphonuclear leukocytes in various stages of degeneration In older lesions epithelioid cells and occasionally giant cells are seen The persistence of heavily staining nuclear fragments at the center of the nodule the end result of a degenerative process termed *chromatotaxis* is said to be characteristic of the glanders lesion Whether the epithelioid cells originate from the connective tissue and other fixed tissue elements or from leukocytes has been disputed

Those animals which survive the initial more acute stages of the infection appear clinically to recover completely They may however succumb later to an exacerbation of pneumonia and at autopsy invariably they show the characteristic pulmonary lesions It is chiefly these occult cases which have been responsible for the spread and persistence of the disease in horses

The control of glanders in animals rests on accurate diagnosis of clinical cases the detection of occult cases and the careful and repeated testing of animals exposed to known sources of infection The most useful means of accomplishing these objectives have been the various tests for sensitivity to mallein and serological tests chiefly that of complement fixation[4] [6] A universally accepted practice has been the ophthalmic instillation of standard mallein which in both patent and occult glanders causes a profuse purulent discharge from the conjunctival sac along with palpebral swelling and cohesion of the eyelids The reaction appears within 5 to 6 hours and may last 24 to 36 hours Subcutaneously administered mallein causes a prompt febrile response in glandered animals and no response in healthy animals Previously healthy animals slaughtered because of positive mallein tests invariably have been found to have typical glanders nodules in the lungs yielding *M mallei* on culture Mallein administered by any method may cause a significant rise in both agglutinating and complement fixing antibodies within 48 hours[4] [5] Blood should therefore be taken for serological examination prior to malleinization With natural infection complement

fixing antibodies appear as early as the second week of the disease and may persist longer than agglutinating antibodies Complement fixation is, therefore the test of choice[43]

Glanders in Man

The occurrence of glanders in man in the past has been in rough proportion to its prevalence in equines and as such has been almost exclusively an occupational disease involving contact with glandered horses and mules and exposure to experimentally infected laboratory animals However transmission from man to man through infected wounds or discharges has been reliably reported [1] as have infections contracted during post mortem examination of human victims[19]

The common mode of infection has always been considered on sufficiently good evidence in most instances, to be by introduction of contaminated material into a wound or onto the abraded skin or mucous membrane However the organism has been shown experimentally to pass across the unbroken skin of guinea pigs[3] Ingestion of infected water or meat also has been a proven source in some human cases and has been demonstrated experimentally in horses[43] Infection through inhalation of contaminated dust or of bacterial clouds accidentally created in the laboratory has in rare instances seemed plausible[6] and has been shown possible in cloud chamber experiments with small laboratory animals[4]

Whether the infectious materials in glanders reaches the lungs and other viscera by direct inspiration by absorption through the pharyngeal mucosa or by passage through the intestine and mesenteric lymph nodes it is impossible to say with certainty in every case The important point is that the nasal and pulmonary discharges as well as the exudates from active lesions and sometimes the urine and feces of animals and humans suffering from glanders are infectious Therefore any other susceptible animal or persons coming into contact directly or indirectly with these discharges is liable to contract the disease in one form or another

Clinical Aspects in Man

By analogy to the disease in animals human infections due to *M mallei* in the past have been called glanders when the nose respiratory

passages and lungs have been the chief sites of disease and farcy when the skin and local lymphatics are primarily involved On critical analysis this classification of acute and chronic forms of two types seems unrealistic since infection with the glanders bacillus in man even more than in equines may manifest itself in a variety of ways over a wide spectrum[4, 7, 8, 9] At one end of this spectrum is the occult type first described by Babes[13] entirely analogous to occult animals glanders in which typical nodules are found in the lungs of persons dying of unrelated causes who may never have shown the clinical signs of this specific infection At the other extreme is the more frequently reported fulminating and widespread pyogenic infection with rapidly fatal septicemia In between lie many clinical types of glanders involving almost any organ or system of the body in a suppurative and granulomatous process It may at first be relatively benign with long periods of relapse and remission but ultimately may flare up into a relentlessly advancing generalized acute infection with a fatal outcome It is thus evident that the so called acute form of glanders has often been the terminal manifestation of the chronic form which in turn may in rare instances have been the sequel of an acute systemic infection which was not immediately fatal

The commonest type of glanders reported in man has in fact been an acute and rapidly fatal illness the incubation period when known varying from a few days to two or three weeks and the total duration from one to three weeks Following the development of an erysipeloid and phlegmonous reaction around the wound of entrance there may be high fever of typhoidal type prostration arthralgias stupor and all the signs of severe intoxication In the inflammatory zone surrounding the initial lesions which may show an early tendency to break down and form ulcers there is the formation of vesicles pustules and at times the development of local gangrene Adjoining lesions may coalesce to form crater like punched out areas with overhanging edges Hemorrhage may occur into or about these lesions Rapidly progressing primary lesions have sometimes been referred to as lupus farcinosus The eruptive process occurring in the primary stage usually is limited in its distribution to the area immediately surrounding the primary lesion or wound entrance from which it arises as a result of direct spread It is not to be confused with the generalized pustular rash which occurs terminally and is due to bloodborn metastases from septic foci The site of primary infection most often has been an extremity but sometimes the face and neck are involved There is frequently a centripetal lymph

angitis with the appearance of abscesses (farcy buds) along the course of the inflamed lymphatic vessels and suppuration of the lymph nodes receiving the drainage On the mucosa of the nose or mouth the lesions at first are similar to those seen on the skin but ulcers form rapidly and may become large They are apt to have the same sharply defined border and to secrete a thick ropy pus mixed with blood Secondary infections are often complicating factors in these locations Frequent sites of ulceration are the nasal septum which may become perforated the palate and the posterior pharyngeal wall Suppurative otitis media, tonsillar abscesses and laryngeal and bronchial ulceration have been reported

In many instances however the site of primary inoculation is never known and the illness becomes evident only with the development of the secondary manifestations These secondary manifestations occurring at varying intervals depending on the rapidity with which the organisms invade the body from the primary focus reflect the spread of infection by the blood and lymph streams There may be acute polyarthritis at first resembling rheumatic fever but ultimately destroying bones and joints in a suppurative process Occasionally however these joint manifestations subside without pus formation Also there may be osteomyelitis periostitis and meningeal involvement

One of the most constant features of glanders in the invasive stage is the formation of intramuscular and subcutaneous nodules which may develop during the second or third week following the initial infection and which may constitute the first evidence of the disease if there has been no obvious primary focus These abscesses are metastatic in origin vary greatly in size and are most often extremely painful Their appearance in some cases has been preceded by sudden sharp pain at the point of subsequent suppuration These lesions contain oily fluid farcy oil or thicker purulent material mixed with blood Partial healing often takes place but extensive breaking down of tissue may occur even when drainage is free The result is extensive cicatricial tissue and sinus tracts secreting a turbid serous fluid It may be stated that these focal abscesses are the commonest lesions in those cases of glanders which run a relatively chronic course over months or years with remissions and exacerbations of the same or new lesions in various locations[60, 61]

Invasion of the lungs may manifest itself by the development of cough productive of sticky purulent sputum occasionally blood streaked and signs of diffuse parenchymal involvement[62, 63] Bronchopneumonia pleurisy with effusion and multiple lung abscesses due to glanders are not infrequently found as prominent features in the more

acute cases[81, 6] On x ray examination the lesions may appear as woolly exudative patches with enlargement of the hilar nodes[84] It has been suggested that less severe forms of glanders may involve at least clinically only the lungs and appear on the x ray film as focal pneumonia [6]

Any of these glanderous processes may continue intermittently for weeks, months or years with exacerbations accompanied by renewed constitutional symptoms progressive emaciation and the usual concomitants of severe chronic infection Amyloid disease has been reported as an occasional finding at autopsy and should be looked for clinically in cases of long standing

Special consideration should be given the characteristic skin eruption of glanders the Hautrotz of the German writers In most cases running a comparatively rapid course or in those cases which have progressed through a chronic course and undergone an acute reactivation of infection the appearance of the cutaneous lesions invariably has heralded a fatal termination The lesions may appear simultaneously over all parts of the body or in successive crops They vary in size appearing first as reddened macules rapidly becoming hard papules on reddened bases surrounded by an area of firm white edema Usually the papule rapidly breaks down centrally to form a vesicle or pustule which subsequently may become umbilicated and by necrosis of the central skin a widening ulceration is formed The evolution of the skin lesions may be extremely rapid as the terminal event over the last few days of life in fatal cases In rare instances the rash does not go beyond the papular stage disappearing with some local desquamation

It is thus evident that glanders in man may assume a large variety of clinical forms causing pathological changes in almost every locality These changes however are fundamentally the result of a fairly uniform process as will be shown later Occult cases of glanders rare in man frequent in the horse may represent the response of the most resistant type of host The frank chronic cases of longer duration appear to have a moderate degree of natural resistance in contrast to those cases which succumb in the early acute stage of the infection Despite these considerations the human species must on the whole be naturally relatively resistant to the glanders organism since the number of cases reported in the past has been extremely small in proportion to the opportunities for infection attendant upon the wide prevalence of animal glanders in years gone by

The mortality among the reported cases of glanders has been at or above 90 per cent and not more than 5 to 10 per cent have recovered

completely from this disease for which heretofore there has been no specific treatment Since the incidence of occult human glanders has never been determined as it has in animals it is entirely possible that the morbidity and mortality have actually been lower than the stated figures It is obvious though that in a case of proven infection with *M mallei* there has up to the present time been very little probability that permanent remission would eventuate However wider experience with chemotherapeutic and antibiotic agents than has been possible in the past due to the rarity of the disease may eventually alter the outlook in some cases

Diagnosis

A history of exposure to glandered animals or their discharges or of handling infected laboratory animals and autopsy material of course leads to a suspicion of this specific infection in individuals showing acute local suppuration with lymphangitis or any signs of a generalized acute febrile illness As might be inferred from the extent and variation of the clinical and pathological processes in glanders there is nothing typical about the disease except perhaps the terminal cutaneous eruption Even this feature has in some cases been readily confused with other pustular eruptions such as variola and varicella secondary syphilis and various other eruptive and granulomatous affections

A positive diagnosis therefore rests ultimately on the isolation and identification of the specific organism The glanders bacilli are found frequently on microscopic examination of stained smears of exudate from relatively fresh draining lesions where they are for the most part extracellular although occasional intracellular organisms are observed They are demonstrated with much greater difficulty in older lesions However *M mallei* is as a rule readily cultured from any open focus of glanders Sputum or exudate suspected of being glanderous may be incubated with penicillin prior to inoculation on standard media containing inhibitory dyes e g crystal violet 1 200 000 these measures serving to minimize the overgrowth of common gram positive contaminants and thereby facilitate the identification of small numbers of *M mallei*[70] Intraperitoneal inoculation of glanders-infected material into male guinea pigs will produce the typical Strauss reaction after 48 to 7 hours Occasionally with a relatively avirulent strain repeated passage through guinea pigs may be necessary to produce the typical acute orchitis[71]

M. mallei can be isolated with comparative ease from the blood in acute cases with septicemic manifestations or in chronic cases undergoing terminal relapse.[11] The organism rarely is recovered in blood cultures during the relatively benign phases of chronic glanders.

Suspected strains may be identified by their characteristic growth on potato medium, by agglutination with known antiglanders serum or by agglutination with the patient's serum if that proves to agglutinate, and by complement with standard glanders antigens. Differentiation from *M. pseudomallei*, most strains of which appear to be antigenically identical with most strains of *M. mallei*, may be accomplished on the basis of motility, gelatin liquefaction and various sugar fermentations.[1,7]

In the serodiagnosis of glanders the complement fixation test has proven to be the most reliable in animals, using either whole killed organisms or extracts of *M. mallei* as antigen.[6, 8] Most of the human cases reported have been too rapidly fatal to allow accurate appraisal of this test; where it has been performed, although it has been reported as positive during the first two weeks in occasional chronic cases.[3, 80] The agglutination test becomes positive relatively early in the course of even acute cases. In those of longer duration the agglutinin titer may appear and fall off more rapidly than the titer of complement fixing antibodies.

Sensitivity to mallein has been used occasionally in the diagnosis of chronic human glanders. As in equines the diagnostic reaction is both local and systemic, a febrile response occurring during the forty eight hours following subcutaneous injection.[13, 11, 81] Some cases, even when glanders has been proven to be present, have not reacted to intradermal mallein.[6] The scratch skin test[3] and the ophthalmic test[86, 4] have been used also with clearcut results in proven cases of glanders. Mallein administered by any route, as in animals, will cause a definite rise in serum antibodies.

Depending on its potency, mallein injected into patients for diagnostic purposes should be diluted to at least 1:100,000 for the first test. The concentration can be increased in successive stages, as with purified tuberculoprotein derivative, until a dilution is reached which will provoke a reaction.

Treatment and Prophylaxis

Claims for successful treatment of active glanders in man with killed vaccines or with mallein and similar products have been wholly unconvincing. Immune serum, arsenicals, bismuth and mercury compounds

completely from this disease for which heretofore there has been no specific treatment. Since the incidence of occult human glanders has never been determined as it has in animals, it is entirely possible that the morbidity and mortality have actually been lower than the stated figures. It is obvious though that in a case of proven infection with *M. mallei* there has up to the present time been very little probability that permanent remission would eventuate. However, wider experience with chemotherapeutic and antibiotic agents than has been possible in the past, due to the rarity of the disease, may eventually alter the outlook in some cases.

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A positive diagnosis therefore rests ultimately on the isolation and identification of the specific organism. The glanders bacilli are found frequently on microscopic examination of stained smears of exudate from relatively fresh draining lesions, where they are for the most part extracellular, although occasional intracellular organisms are observed. They are demonstrated with much greater difficulty in older lesions. However, *M. mallei* is as a rule readily cultured from any open focus of glanders. Sputum or exudate suspected of being glanderous may be incubated with penicillin prior to inoculation on standard media containing inhibitory dyes, e.g. crystal violet 1:100,000, these measures serving to minimize the overgrowth of common gram positive contaminants and thereby facilitate the identification of small numbers of *M. mallei*.[8] Intraperitoneal inoculation of glanders-infected material into male guinea pigs will produce the typical Strauss reaction after 48 to 72 hours. Occasionally with a relatively avirulent strain repeated passage through guinea pigs may be necessary to produce the typical acute orchitis.[11]

to assess the value of the newer antibiotics aureomycin and chloromycetin in the treatment of glanders

Since complete recovery from glanders is rare in man the question of immunity to reinfection with M mallei has never been elucidated It has been noted not infrequently that in horses the disease may subside completely with apparent clinical recovery even to the loss of sensitivity to mallein These cases however in many instances have proven to harbor latent infection There being no effective vaccine against glanders for either human or veterinary use the control of the disease has thus rested entirely on the detection of active and occult cases of glanders in equines and their previously healthy contacts through the use of the mallein and the serological tests Many states have laws requiring the prompt reporting of suspected cases and providing for indemnity for animals destroyed under official direction because of proven disease The prevention of glanders in man therefore still is directly dependent on its continued suppression in animals

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have been of no value Improvement in some cases has been correctly ascribed to supportive and symptomatic treatment Surgical intervention for apparently localized foci of glanders infection is a matter of careful judgment since in many instances attempts at radical excision in chronic glanders have done more harm than good

In recent years however there have been rare opportunities for the assessment of sulfonamide compounds and antibiotic agents in the treatment of glanders and melioidosis All strains of *M mallei* and *M pseudomallei* thus far tested have been found to be insensitive in vitro to the action of penicillin which in no case has altered the clinical course of human infection with either organism The sensitivity of one strain of *M pseudomallei* to sulfadiazine has been found comparable with that of the pneumococcus in vitro[88] and this drug appears to be effective in the treatment of glanders and melioidosis in experimentally infected laboratory animals[9] In at least one case of suspected though unproven glanders [9] and in four cases of melioidosis[90, 91] sulfonamides have produced a suggestive clinical response *M mallei* and *M pseudomallei* have both been found initially sensitive to streptomycin in vitro the latter organism however rapidly developing marked drug resistance[9] One case of combined chronic osseous glanders and tuberculosis has been reported recently in which there was some evidence to suggest that streptomycin had eliminated *M mallei* from the lesions[83] In this case an acute febrile reaction similar to the Herxheimer reaction seen in syphilotherapy occurred within forty eight hours after institution of streptomycin treatment with aggravation of joint manifestations The organism could not be recovered after the first course of streptomycin In contrast is a recently reported instance of chronic melioidosis in which penicillin sulfadiazine and streptomycin were all ineffective clinically and where the strain of *M pseudomallei* isolated from the lesions was highly resistant to all three chemotherapeutic agents in vitro

It would seem logical therefore from limited clinical and laboratory experience thus far gained in the chemotherapy of glanders and melioidosis that any form of infection with *M mallei* should be treated promptly with sulfadiazine in full dosage Where this drug causes no noticeable response streptomycin should be given also in daily parenteral doses of at least [illegible] grams keeping in mind the ever present danger of the development of drug resistance on the part of any strain initially sensitive Parenteral penicillin therapy is definitely indicated where active secondary infection of open glanders lesions is demonstrated to be due to penicillin sensitive organisms[83] There has as yet been no opportunity

to assess the value of the newer antibiotics aureomycin and chloromycetin in the treatment of glanders

Since complete recovery from glanders is rare in man, the question of immunity to reinfection with *M mallei* has never been elucidated It has been noted not infrequently that in horses the disease may subside completely with apparent clinical recovery even to the loss of sensitivity to mallein These cases however in many instances have proven to harbor latent infection There being no effective vaccine against glanders for either human or veterinary use the control of the disease has thus rested entirely on the detection of active and occult cases of glanders in equines and their previously healthy contacts through the use of the mallein and the serological tests Many states have laws requiring the prompt reporting of suspected cases and providing for indemnity for animals destroyed under official direction because of proven disease The prevention of glanders in man therefore still is directly dependent on its continued suppression in animals

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CHAPTER VIII-A

MELIOIDOSIS

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Synonyms.—Stanton's disease, glanders-like disease of Rangoon, pneumo-enteritis.

Definition.—Melioidosis is an infectious disease closely resembling glanders and characterized by an initial fever, diarrhœa, vomiting and collapse, succeeded if recovery occurs from the acute stage, by fever, septicæmia and abscess formation in the lungs, liver, kidneys and other organs. The disease is caused by a bacterium, *Bacillus whitmori*, and is primarily an infection of rats and other rodents.

History

Melioidosis was first described by A. Whitmore and Krishnaswami (1912) as occurring in destitute individuals autopsied at Rangoon. It was next recognized in the Federated Malay States. Fletcher (1913) encountering it in the form of a severe epizootic in guinea pigs in the laboratory at Kuala Lumpur. In 1917 Stanton described human infections at Kuala Lumpur and in 1924 Stanton and Fletcher published an excellent description of the disease. The causative organism was isolated by A. Whitmore (1913) who named it *Bacillus pseudomallei*, but as this name had been used for another organism, Stanton

and Fletcher (1921) proposed for it the name *Bacillus whitmori*, which has since been adopted

Geographical Distribution

Since the discovery of this disease, 65 cases have been recognized all but three in Burmah and the Federated Malay States In 1927, Pons and Advier described a case in Indo China, observed in 1925 while Vielle, Morin and Massias (1926) observed a second case in the same country Denny and Nicholls (1927) have observed a case in Ceylon While the geographical distribution of this disease would appear to be very limited, its resemblance to glanders and tularæmia may have caused many mistakes in diagnosis, and it may have a much more wide spread distribution than is evidenced by the available data

Etiology

Melioidosis is caused by a bacillus closely resembling *Bacillus mallei* known as *Bacillus whitmori* It is a delicate rod with rounded ends and occurs in all of the lesions and discharges in large numbers It is Gram negative non acid fast easily grown upon common laboratory media and actively motile It is an obligate aerobe and produces no gas in carbohydrate media Some culture show chromogenic reactions the color varying from a yellow to brown It stains more deeply at the ends than in the middle with Giemsa s stain and resembles *Bacillus pestis* in this respect Upon glycerin agar this bacillus appears to form two distinct colony forms one in which the colonies appear shrunken and corrugated the rough form and one in which the colonies have a smooth slimy mucoid appearance the smooth form These forms are serologically identical It liquefies gelatine and does not form indol in peptone water

Bacillus whitmori is able to live outside the body for long periods of time, if temperature conditions are favorable Cultures mixed with soil from a vegetable garden survived for 27 days mixed with tap-water or ditch water for as long as 44 days and with feces and normal saline for 27 days Virulent bacilli have been isolated from urine after 17 days and from a decomposing guinea pig after 8 days The organism is very sensitive to disinfectants and to high and low temperatures and apparently thrives best in tropical and sub tropical climates

Animals may be infected through the skin by scarification by subcutaneous inoculation by feeding or by spraying into the respiratory passages Guinea pigs, rats, mice, rabbits dogs cats, goats, sheep and monkeys have been

experimentally infected and in all of these animals death has occurred although the disease is most fatal to rodents especially to rats Attempts to infect the horse have been unsuccessful

Epidemiology

Melioidosis primarily is a disease of rodents especially of rats although natural infections occur in mice guinea pigs rabbits and rarely in dogs and cats Rats apparently are the chief reservoir of infection and these animals are infected by consuming food contaminated with the urine of infected rats as the bacillus occurs in the urine in large numbers The method of infection in man is unknown but Stanton and Fletcher (1924) and Whitmore (1913) believe that it occurs through the alimentary tract and suggest that it is caused by eating food contaminated by the excreta of infected rodents The disease is not contagious from man to man so that segregation of cases is not necessary and there is no instance of the transfer of the disease from man to man although all cases have been treated in open wards in hospitals This is the more surprising as the bacillus is found in the sputum urine and discharges from the skin lesions of patients suffering from the disease and is able to survive for days in these substances

While melioidosis closely resembles glanders there is no evidence that the horse has anything to do with the transference of the infection to man as the disease cannot be experimentally transmitted to the horse A transient nasal infection in a horse was noted by Stanton Fletcher and Symonds (1927) the first instance in which *Bacillus whitmori* has been found in this animal

Pathology

The characteristic lesion of melioidosis is a caseous nodule at first so small as to be invisible to the naked eye but which increases in size until it becomes visible as a mass of caseous material surrounded by an inflammatory margin In properly stained sections many irregular clumps of chromatin may be observed scattered throughout the caseous mass representing the broken down nuclei of the necrosed tissue cells

In man these nodules may be found in practically every tissue and organ with the exception of the brain In the lungs large caseous areas are produced by the coalescence of the nodules but abscess formation is rare while in the liver irregular caseous areas are produced by the coalescence of the nodules many of which suppurate and form abscesses In the spleen which is enlarged and in the kidney abscess formation occurs and caseous nodules are observed frequently The gall bladder urinary bladder, the subcutaneous tissues the

muscles and the bones all may present caseous nodules or abscess formation

Bacillus whitmori may be recovered from all the lesions and from the blood and from the urine in those cases in which the kidney or bladder are involved Small ulcerative lesions have been observed in the cæcum but as *Bacillus whitmori* could not be isolated from these ulcers, it is doubtful if these lesions were produced by this organism

The mechanism of the production of the lesions in this disease is unknown The causative agent *Bacillus whitmori* does not produce an exotoxin or hemolysin in cultures nor does the injection into the skin or other tissues of sterilized extracts of the organism produce marked inflammatory reaction or destruction of tissue

SYMPTOMATOLOGY

The symptomatology of melioidosis varies so much that it is impossible to diagnose the infection unless *Bacillus whitmori* can be demonstrated in the suspected lesions or in the blood urine or exudates According to Stanton and Fletcher (1924) some of the acute cases resemble plague or cholera others may resemble malaria pulmonary tuberculosis or typhoid fever while still others may resemble glanders tertiary syphilis or tuberculosis of the bones

The onset may be very sudden with vomiting diarrhœa and collapse or more gradual with high fever and the usual symptomatology of a septicæmia or of typhoid fever Pulmonary involvement usually is present, evidenced by cough discomfort or pain in the chest more or less dyspnœa and the physical signs of a bronchitis or broncho pneumonia Most patients die within a week, but in those who live for a longer time abscesses may develop in the subcutaneous or muscular tissues or in the bones and a pustular eruption somewhat resembling that of small pox has been described as occurring in this infection The cases which commence suddenly with vomiting and diarrhœa and which die in collapse within a short time greatly resemble cholera, while those that rapidly develop an intense septicæmia resemble plague

COMPLICATIONS AND SEQUELÆ

Owing to the rapid course and extreme fatality of melioidosis little is on record as to the occurrence of complications or sequela In one patient, who recovered from the acute infection Stanton and Fletcher (1924) noted a condition of invalidism accompanied by abscesses and chronic suppuration of the bones of the legs and feet existing two years after the commencement of the disease

Prognosis

The prognosis of melioidosis is exceedingly grave Of the 65 cases of the disease described in the literature only two recovered and one of these as mentioned above still presented serious lesions two years after the acute symptoms had disappeared

Diagnosis

As already noted a diagnosis of melioidosis based upon clinical symptoms alone is impossible Reference has already been made to the resemblance of this infection to numerous other diseases and a diagnosis can be made only by the demonstration of *Bacillus whitmori* in the blood urine exudates or tissues of the infected individual Fletcher (1930) states In practice a correct diagnosis has been made during the life of the patients in only 7 of the 65 cases of which records are available In three cases *B whitmori* was cultivated from the blood in one from the urine in one from a pustular eruption in another from an abscess in the parotid and in the seventh from an abscess in the leg

The above quotation from Fletcher indicates the methods which are available for the laboratory diagnosis of this disease The cultivation of *Bacillus whitmori* from the blood urine exudates or lesions should be attempted always and guinea pigs should be inoculated with blood or pus and observed for the development of the infection which in these animals develops rapidly and is fatal The agglutination test may be of service in diagnosis in patients who live for two or three weeks but in most cases agglutinins are not present early enough in the disease to be of value in diagnosis

If the diagnosis is not made before death has occurred guinea pigs should be inoculated with splenic pulp and cultures should be made from the lesions present in the spleen and other organs Sometimes *Bacillus whitmori* may be present in sufficient numbers in smears of pus from the abscesses or in exudates to render a tentative diagnosis of melioidosis possible but such a diagnosis always should be confirmed by the cultivation of the causative organism from the blood urine exudates or tissue lesions

Prophylaxis

As melioidosis is a disease of rodents especially of rats the destruction of these pests and protection of food from contact with them are valuable methods of prophylaxis There is no evidence that this infection is contagious or that direct infection from man to man ever occurs, so that the segregation of patient

suffering from the disease is not necessary We are entirely ignorant of the manner in which man becomes infected, but the concensus of opinion is that it is through contaminated food or drink

Treatment

Treatment is purely symptomatic as we have no specific remedy for this disease Attempts to evolve a curative serum or a prophylactic or curative vaccine have so far resulted in failure

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CHAPTER VIII-B

OROYA FEVER AND VERRUGA PERUANA

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Synonyms.—Carrion's disease.

Definition.—Oroya fever and verruga peruana are now considered to be identical and are caused by an organism known as *Bartonella bacilliformis*. The infection is divided into an acute febrile stage known as Oroya fever, characterized by irregular fever, profound anemia, tender spleen and long bones, severe pain in the muscles and bones and glandular enlargement, and a more chronic stage known as verruga peruana, characterized by a peculiar eruption of cutaneous nodules somewhat resembling those of yaws, slight fever and pains in the articulations. The acute initial stage may be absent, the symptoms of the verruga stage being present from the beginning of the attack.

History

Oroya fever and verruga peruana have been known in the valleys of the Andes, especially in Peru, for many centuries and had been generally considered by the medical profession of South America to be different stages of the

same disease until the observations of Strong and his colleagues (1913) apparently demonstrated that they were distinct and that the peculiar organism first found in the red blood corpuscles by Barton (1909) was the cause of Oroya fever but not of verruga peruana However, the more recent observations of Noguchi (1926–1928) which have been confirmed by others have demonstrated beyond doubt that verruga peruana is simply one stage of the disease called Oroya fever and that *Bartonella bacilliformis* is the cause of the clinical picture and pathological lesions in both conditions In view of the identity of these two so called diseases it would be better to abandon the terms Oroya fever and verruga peruana and use the synonym Carrion's disease' as the designation of the condition and this name will be used in the following description

Geographical Distribution

Carrion s disease (Oroya fever and verruga peruana) occurs in Peru Ecuador, Chile and Bolivia being confined to the narrow, deep valleys of the western slopes of the Andes at altitudes varying from 1,500 to as much as 10,000 feet It appears to be locally confined to the hot contracted, ravine like valleys, where the air is stagnant and there is little or no wind while the more open windy valleys in close proximity remain free from the disease In Peru the states of Ancachs Cajamarca Lambayeque Libertad and Lima are known endemic areas

Etiology

Although this disease has been known in Peru since the conquest of that country by Pizarro and the two stages of the disease called Oroya fever and verruga peruana were regarded as manifestations of the same disease by local physicians the first serious experimental effort to solve the question of identity was that of Carrion, a medical student in Lima who, in 1885 inoculated himself with blood from a verruga nodule and about one month later developed Oroya fever from which he died This experiment confirmed the belief of Peruvian physicians in the identity of the two conditions but in 1913 Strong and his colleagues produced an attack of verruga peruana in a volunteer after the inoculation of material from verruga lesions but with none of the preliminary symptoms of Oroya fever They concluded that Oroya fever and verruga peruana were distinct diseases and it was not until the conclusive observations of Noguchi (1926–1928) established their identity that the question was solved In a long series of classical experiments upon monkeys Noguchi proved that in these animals the inoculation of material from the lesions of verruga peruana

can produce a severe acute febrile disease identical with Oroya fever and he was able to isolate *Bartonella bacilliformis* from nodules that afterward developed in these animals and to produce with cultures the anemia and other symptoms typical of Oroya fever Noguchi's observations have been confirmed by Mayer and Kikuth (1927) Da Cunha and Muniz (1927) and Gaillard and Kobles (1928)

The causative organism of Carrion's disease was first described by Barton (1905-1909) as rod like motile bodies within the red blood corpuscles sometimes as many as 30 per cent of these corpuscles being infected Barton's work was confirmed by Castiaburro and by Darling and in 1915 Strong also confirmed the presence of this organism in the blood in Oroya fever named it *Bartonella bacilliformis* and stated that it was the cause of Oroya fever In 1926 Noguchi and Battistini obtained *Bartonella bacilliformis* in pure culture from blood taken during life from a fatal case of Oroya fever and produced both the typical symptoms of this fever and the nodules of verruga peruana in monkeys inoculated with these cultures In the endothelial cells of the verrugous nodules they demonstrated the organism and were able to cultivate it from the nodules in the experimental animals

The organisms in the red blood corpuscles are very pleomorphic rodlike V forms Y forms curved or straight cross-forms and rounded forms being present while in the endothelial cells the rounded forms are constant each containing a mass of chromatin The organism stains with the Wright or Giemsa stain the cytoplasm staining blue with the ends more intensely stained In some of the rods a reddish or deep purple dot may be seen at the end or near the end of the rod and many such organisms occur in chains It is Gram negative sluggishly motile and the rods measure from 1 5 to 2 5 microns in length the rounded forms from 0 5 to 1 micron in diameter While there is not unanimity of opinion most observers believe that these organisms are bacterial in nature From one to four flagella may be present at one end The organisms isolated in culture from the verruga nodules are identical morphologically culturally and serologically with those isolated from the blood in the Oroya fever stage of Carrion's disease

Pinkerton (1937) Weidman and Pinkerton (1938) Jiminez and Buddingh (1940) and Howe (1942) have all cultivated *Bartonella bacilliformis* upon various culture media and the latter obtained an agglutinating serum by injections of the living cultures into rabbits The best results in cultivation have been obtained when the organism is cultured in developing chick embryos but Geiman (1941) employing a liquid tryptone serum medium containing ascorbic acid has obtained luxuriant growths of *Bartonella bacilliformis* Noguchi in 1926 was the first to cultivate this parasite upon his Leptospira medium

In the swollen endothelial cells of the spleen liver kidneys and lymph nodes the bartonella occur in masses and in fatal cases the blood and lymph vessels of

same disease until the observations of Strong and his colleagues (1913) apparently demonstrated that they were distinct, and that the peculiar organism first found in the red blood corpuscles by Barton (1909) was the cause of Oroya fever but not of verruga peruana However, the more recent observations of Noguchi (1926 19 8) which have been confirmed by others, have demonstrated beyond doubt that verruga peruana is simply one stage of the disease called Oroya fever and that *Bartonella bacilliformis* is the cause of the clinical picture and pathological lesions in both conditions In view of the identity of these two so called diseases it would be better to abandon the terms Oroya fever and verruga peruana and use the synonym Carrion s disease as the designation of the condition and this name will be used in the following description

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Carrion s disease (Oroya fever and verruga peruana) occurs in Peru Ecuador, Chile and Bolivia being confined to the narrow, deep valleys of the western slopes of the Andes at altitudes varying from 1,500 to as much as 10 000 feet It appears to be locally confined to the hot contracted, ravine like valleys, where the air is stagnant and there is little or no wind while the more open windy valleys in close proximity remain free from the disease In Peru the states of Ancachs, Cajamarca Lambayeque, Libertad and Lima are known endemic areas

Etiology

Although this disease has been known in Peru since the conquest of that country by Pizarro and the two stages of the disease called Oroya fever and verruga peruana were regarded as manifestations of the same disease by local physicians the first serious experimental effort to solve the question of identity was that of Carrion a medical student in Lima who in 1885 inoculated himself with blood from a verruga nodule and about one month later developed Oroya fever from which he died This experiment confirmed the belief of Peruvian physicians in the identity of the two conditions but in 1913 Strong and his colleagues produced an attack of verruga peruana in a volunteer after the inoculation of material from verruga lesions but with none of the preliminary symptoms of Oroya fever They concluded that Oroya fever and verruga peruana were distinct diseases and it was not until the conclusive observations of Noguchi (1926–1928) established their identity that the question was solved In a long series of classical experiments upon monkeys Noguchi proved that in these animals the inoculation of material from the lesions of verruga peruana

by Battistini (1931) who produced infection in a monkey by the bites of sand flies afterwards recovering *Bartonella bacilliformis* from the blood of the animal He also was able to demonstrate this parasite in the flies by obtaining pure cultures of the organism from them and produced infections in monkeys by the inoculation of crushed naturally infected sand flies In his experiments *Phlebotomus noguchii Phlebotomus verrucarum* and *Phlebotomus peruensis* were all capable of transmitting the infection

While up to the present time no successful transmissions of this infection have been accomplished in man the work of Hertig (1942) who was successful in producing the disease in monkeys by the bites of *Phlebotomus verrucarum* definitely demonstrate that it is transmitted by infected sand flies Hertig used in his experiments wild sand flies *Phlebotomus verrucarum* which were caught in a verruga zone and brought to Lima where the experiments were performed He allowed these flies to bite 8 monkeys and of these 5 became infected with *Bartonella bacilliformis* No skin lesions were produced in these animals but the infection was proven by blood cultures the production of the infection in other monkeys by these cultures and by immunity tests Several species of South American monkeys were infected by the inoculation of cultures and in some of these animals nodules were produced from which the organism was recovered

In the examination of the proboscis of sand flies caught in verruga regions Hertig found massive infections with organisms resembling *Bartonella bacilliformis* in the tip of the proboscis in both males and females and the proportion of sand flies found infected was frequently as high as 40 to 50 per cent The source of the infection in these flies is unknown and the fact that males were found infected indicates that it must have been obtained from other liquids than blood for the males do not suck blood Cultures of this organism do not produce verruga when inoculated and Hertig concludes that the data thus far are insufficient to make clear the extent to which bartonella enters into these infections and whether or not they represent the mechanism of transmission of Carrion s disease although he was successful in cultivating *Bartonella bacilliformis* from the proboscis of 2 sand flies

PATHOLOGY

In patients dying of Carrion s disease during the Oroya fever stage the skin presents the pale yellowish color noted in pernicious anemia there is general glandular enlargement with slight edema and the spleen and liver are enlarged Microscopically the liver shows areas of degeneration and central necrosis around the hepatic veins while a considerable amount of yellow pigment is noted in the degenerated areas

The spleen presents areas of degeneration and numerous infarcts while ir

many internal organs may be distended by large masses of the organisms while in the endothelial cells of the cutaneous verruga nodules the bartonella are found also but in much smaller number than in the internal organs

There is a close resemblance between the bartonellae and the rickettsiae, but they are considered to be distinct by the best modern authorities

Epidemiology

Carrion s disease occurs between 7° and 17° South Latitude in the windless valleys situated in the deep canons of the west slopes of the Andes Mountains It is observed most commonly between January and April especially in the warm rainy season Strong observed that during June, July and August the Oroya fever stage of Carrion s disease was seldom seen but the verruga stage was prevalent at that time as would be expected, if the latter were a late stage of the former as is the case No age is exempt and it occurs in all races and in both sexes

The infection is most liable to be contracted after sundown and while cases are more numerous among those residing for some time in the endemic area travellers passing only one night in such regions have been infected The disease first attracted general attention in 1870 when it is stated that over seven thousand workmen engaged in the construction of the railway between Lima and Oroya perished from this infection The disease is most prevalent in laborers upon construction programs or in the rural districts

Carrion's disease is undoubtedly transmitted by arthropods and recent observations have demonstrated that certain species of sand flies are the usual transmitting agents Noguchi Shannon Tilden and Tyler (1929) attempted to transmit Carrion s disease (Oroyo fever) to monkeys by the injection of the crushed arthropods in saline solution collected in the endemic regions of the disease and obtained negative results with ticks mites lice fleas bedbugs mosquitoes buffalo gnats and midges As Townsend in 1912 and 1914 had stated it as his belief that the sand fly *Phlebotomus verrucarum* from experimental and epidemiological evidence was the vector of this infection Noguchi and his colleagues experimented with *Phlebotomus verrucarum* *Phlebotomus noguchii* and *Phlebotomus peruensis* and were able to obtain cultures of *Bartonella bacilliformis* from the blood of monkeys inoculated with the crushed insects and these animals were immune after recovery to inoculation with cultures of this parasite obtained from human beings suffering from Carrion's disease These investigators concluded that *Phlebotomus noguchii* is certainly a vector of *Bartonella bacilliformis* *Phlebotomus verrucarum* is probably a vector, and *Phlebotomus peruensis* is doubtful as a vector

The observations of Noguchi and his colleagues have been confirmed recently

The characteristic feature of the acute stage of Carrion s disease is the very rapid development of anemia and the changes in the blood picture Within three or four days the erythrocyte count may fall to 1 000 000 cells per cu mm or even lower accompanied by hemic murmurs, tachycardia and dyspnea The morphological character of this anemia is that of the pernicious form and in severe cases megaloblasts are present in large numbers while even in the case of average severity these cells are present in small numbers and normoblasts and poikilocytes are numerous There is a marked leucocytosis usually present, often exceeding o ooo leucocytes per cu mm The differential count is normal but myelocytes and immature neutrophiles are present The color index is above 1 Polychromatophilia is marked in the severe infections

The causative organism is present in very mall numbers in the erythrocytes in the milder cases and it is often necessary to resort to culture methods in order to demonstrate them but in severe cases the organism is present in great numbers and may be easily demonstrated in either fresh or stained prepa rations of the blood

In the acute stage of this disease the liver spleen and lymph nodes are enlarged and the superficial lymph nodes easily palpable As anemia de velops marked edema of the legs and around the joints appears and albumin may occur in the urine The kidneys do not appear to be seriously injured and show no lesions at autopsy aside from congestion and cloudy swelling Consti pation usually is present, but diarrhea may develop in the severe cases toward the latter portion of the illness or just before death

The symptoms of the chronic or verruga stage of Carrion s disease usually app ar in from two to six weeks following the acute stage or they may appear without having been preceded by the acute stage It is probable that in such cases the acute stage symptoms were so mild as to be overlooked or were wrongly diagnosed and that in all cases of Carrion s disease there is an acute stage however mild the symptoms may have been

The onset of the chronic or verruga stage is characterized by pains in the ankles knees elbows and wrists accompanied by a fever ranging between 100 F and 104° F (37 8° to 40° C) but usually not exceeding 103° F (39 3° C) There is headache muscular pain and sorene s and considerable prostration but no enlargement of the liver spleen or lymph nodes The febrile period is of short duration and is terminated with the appearance of the eruption which may be discrete or abundant and most marked on the extensor surfaces of the legs and arms and on the face although it may occur on the trunk and on the palms of the hands and the soles of the feet The distribution varies with the type of the eruption to a certain extent and the duration of the eruption covers from several weeks to several months the average duration being two to three months

Several varieties of verruga eruption have been described but it should be

regular masses of yellowish pigment are noted in the necrotic areas, between the cells of the pulp and in the endothelial cells, the Malpighian bodies being normal in appearance The heart may be enlarged and ecchymotic, the muscular tissue being pale in color and reduced in consistence The bone marrow is red in color soft and necrotic and there is marked proliferation of the endothelial cells which contain large numbers of bartonellae The blood shows a very marked anemia the blood picture being that of a pernicious anemia with marked increase in the polymorphonuclear leucocytes and a practical absence of eosinophiles

The pathology of the verruga stage of Carrion s disease consists largely in a proliferation of the endothelial cells of the lymphatics and a blocking of the lymphatic channels by fibroblasts and plasma cells the capillaries being congested and dilated The nodules somewhat resemble those of yaws but are much more vascular bleed easily and collections of angioblasts are noted around the blood vessels

In the older and larger nodules fibroblasts are found in the collections of endothelial cells and the resulting picture is that of a fibrosarcoma, or if the connective tissue is less in amount the structure may resemble that of a myxosarcoma or an angioma

Symptomatology

The incubation period in man is about three weeks and the onset is rather gradual being marked by malaise headache general muscular aching and chilly and feverish sensations Following these prodromal symptoms anemia rapidly develops the fever rises to 101 F or 102° F (38 4° to 38 9° C), rarely to 104° F (40° C) the headache and pains in the muscles increase in severity, and many patients complain of deep seated pains in the bones Pressure over the bones especially over the sternum demonstrates that there is marked tenderness undoubtedly due to the marked pathological changes occurring in the bone marrow The joints often are tender and painful and the patient, in the severe types of the disease usually is delirious A fulminant form of the infection occurs in which the symptoms resemble those of typhus, and death may occur within a few days preceded by delirium insomnia and coma Cases may be mild in character and it is probable that these mild infections are often unrecognized

The fever in the acute stage (Oroya fever stage) of Carrion's disease is remittent and irregular in type and seldom reaches 104° F (40° C) In some cases it is intermittent in character and may be confused with the temperature curve of malarial infections The febrile paroxysms often are prolonged over several weeks resembling typhoid or paratyphoid fever An eruption does not occur except in the very severe or fulminant cases when petechial spots may be observed, and hemorrhage may occur from the gums

and Hurtado (1938) have found *Bartonella bacilliformis* in the blood of apparently healthy individuals

Howe (1943) has demonstrated that agglutinins may occur in the blood in this infection but that a measurable titre is not produced in all individuals suffering from the infection The titre of the agglutination usually reaches it peak just before the appearance of the eruption and agglutins disappear with the disappearance of the eruption He found that in many patients the bartonella could be recovered from the blood even after the disappearance of agglutinins and that non immune individuals who had received formaldehyde treated vaccine developed agglutinins but that these did not prevent infection when such persons were exposed in a verruga locality During the time that agglutinins are present in the blood an agglutination test may be of value in diagnosis Negative reactions are of no value whatever

Complications and Sequelæ

No complications have been described as occurring in the Oroya fever stage of Carrion s disease but in the verruga stage secondary invasion of the nodules by bacteria may lead to localized infection and necrosis or to a general septicemia Severe hemorrhage sometimes occurs from the verruga nodules which may endanger life As the infection may last for several months it may be complicated by numerous other diseases No sequelæ of importance have been described

Diagnosis

The diagnosis of the Oroya fever stage of Carrion s disease depends upon the demonstration of the causative agent *Bartonella bacilliformis* within the red blood corpuscles The clinical picture of anemia superficial lymph node enlargement and fever while suggestive is not diagnostic but if the patient gives a history of residence in the endemic areas these symptoms warrant a tentative diagnosis, which should be confirmed by a blood examination if possible Blood smears should be stained with the Wright or Giemsa stain as in malaria and the parasites usually are present in sufficient numbers to enable a diagnosis to be made If the blood should be negative which very rarely occurs smears of juice obtained by puncture of an enlarged lymph node will show rod shaped and rounded forms of the parasite when properly stained Blood cultures are recommended by Noguchi as more reliable than blood examinations when the parasites are few in number

The diagnosis of the verruga stage of Carrion s disease is very easy as the verruga nodules are characteristic The conditions most apt to be confused with the verruga stage are yaws and molluscum contagiosum

understood that all varieties may occur upon the same patient and in different stages of development In this respect the infection resembles yaws, and, as in yaws, the various types of granulomata may be undergoing involution at the same time that new granulomata are being evolved

Two types of eruption are usually described the *miliary*, in which the lesions do not exceed a small pea in size, and the *nodular* in which the lesions are much larger measuring as much as 5 to 7 mm in diameter

The *miliary rash* develops as pinkish macules or papules minute in size which gradually become nodular and of a darker color When fully developed they may be a dusky or bright cherry red in color and are often slightly pedunculated and smooth and shining in appearance After persisting for a variable period of time these lesions dry up and disappear without leaving a scar This type of eruption occurs most frequently on the face and extensor surfaces of the extremities but may occur also upon the mucous membranes of the mouth conjunctivae nose pharynx esophagus intestine, stomach bladder uterus and vagina

The *nodular* type of eruption develops more slowly than the miliary and individual granulomata may be as large as a pigeon s egg These lesions usually are discrete but may join forming large fungating masses Necrosis and ulceration due to strangulation or secondary bacterial invasion frequently occur and life may be endangered from hemorrhage or septicemia The nodules bleed easily when injured and are firm in consistence They are cherry red in color and are not covered with a crust unless ulceration has occurred the surface being smooth and polished in appearance This type of eruption does not occur upon the mucous membranes but most frequently about the flexures of the extremities especially the knees and elbows although it also occurs upon the legs and arms

In some cases subcutaneous nodules develop which may involve the skin resulting in ulcerations of considerable extent These lesions are known as *mulaire* verrugas

The verruga eruption appears in successive crops and in mild infections the miliary type only may appear Healing of the ulcerated granulomata may be followed by disfiguring scars but the miliary and nodular lesions when uncomplicated by ulceration gradually dry up and disappear without leaving a scar

Infection with *Bartonella bacilliformis* probably exists without the occurrence of the typical nodules or symptoms Strong (1944) says "the writer still inclines to the opinion that in man just as in animals bartonella infection may sometimes pursue its entire course without the appearance of a verrucous eruption and either terminate in death or recovery ' E Escomel (1938) reported a case in which no eruption ever occurred and Mackehenie and Battistini and Weinman

had the disease They were inoculated subcutaneously with this vaccine before being stationed in a verruga zone During the following 7 months these men were examined repeatedly blood cultures being made and their blood serum being tested for agglutins Agglutins appeared in their blood after vaccination but from the blood of 12 or 55 per cent *Bartonella bacilliformis* was obtained in cultures thus proving that the vaccine had not prevented infection Five of the 12 individuals developed a mild eruption and all 12 suffered from mild systemic symptoms due to their infection Howe and Hertig concluded that while the vaccine did not prevent infection it did render it much milder in character and was therefore beneficial

TREATMENT

There is no specific treatment for Carrion s disease In the acute or Oroya fever stage small doses of the arsphenamines not exceeding 0 3 gm intravenously have been used with some success and the same treatment has been used in the verruga stage but with less favorable results The nodules in the verruga stage if necrotic or septic should be excised and care should be taken to avoid traumatism as the nodules sometimes bleed very freely and the hemorrhage may even endanger life The application of compresses or styptics will control such hemorrhages During the acute febrile stage the patient requires most careful nursing and the treatment is largely symptomatic The use of tonics as iron and arsenic is indicated throughout the verruga stage of the disease

Kikuth (1937–1938) has recommended an arsenic antimony compound called S D T 386 B in the treatment of this infection and reported that Manrique obtained good results with it in the treatment of 14 cases of Oroya fever in Peru employing doses of 0 1 to 0 3 gm 2 or 3 times and that after such treatment the bartonella disappeared from the blood but his results have not been confirmed and it is the opinion of most Peruvian physicians that we possess no specific for this infection

Howe (1943) has treated 3 cases of Oroya fever with an immune serum of high agglutin titre prepared by intravenous administration of bartonella into rabbits and with reported good results in destroying the organisms in the blood stream

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Yaws is initiated by a primary lesion, the mother yaw, and is followed by a generalized eruption of lesions identical with the primary one The yaw granuloma is covered with a dirty yellow or yellowish brown crust, having a rough surface which, when removed reveals a moist granulating nodule exuding a clear viscid serum The verruga nodules are not covered with a crust are red in color and have a smooth shining surface *Treponema pertenue* may be easily demonstrated in the serum exudate of the yaws lesion, and the Wassermann test is positive while in verruga the Wassermann test is negative and *Treponema pertenue* is absent

Molluscum contagiosum can be easily differentiated by the presence of the "molluscum bodies upon microscopical examination of sections of the lesion

It should be remembered that the Oroya fever and verruga stages of Carrion's disease may co exist

Prognosis

The prognosis of Carrion's disease during the Oroya fever or acute stage is bad According to different authorities mortality may vary from 30 to 98 per cent, but it is probable that it does not usually exceed 40 to 50 per cent The prognosis of the verruga stage is excellent as the infection is never fatal in uncomplicated cases during this stage of the disease

Prophylaxis

As Carrion s disease is apparently transmitted by sand flies, the prophylaxis consists in isolation and protection of the patient from the bites of these insects the protection of the healthy from the bites and the destruction of the flies and their breeding places Unfortunately owing to the habits of the sand flies and the character of the habitations of the natives in regions where the disease occurs as well as their economic and cultural condition very little can be accomplished at the present time in the way of prophylaxis Travellers should avoid the endemic areas

The discovery of the efficiency of DDT in destroying sand flies has provided us with an efficient method of killing these flies and its use undoubtedly will reduce markedly the incidence of Carrion s disease if it is properly employed The reader is referred to Chapter XXXIII on 'Malaria' for details regarding the use of this agent but the spraying of cracks in walls caves and the walls and ceiling of rooms with DDT residual spray will be found effective as a prophylactic measure

The use of a formalized vaccine prepared from cultures of bartonella has been followed by Howe and Hertig (1943) in a detachment of 22 guards who had not

CHAPTER IX

TETANUS AND GAS GANGRENE

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Definition.—Tetanus, also known as lockjaw and trismus, is an infectious disease resulting from contamination of wounds and raw surfaces with the *Clostridium tetani (Bacillus tetani)* and/or its spores. The spores under approximate conditions proliferate or germinate giving rise to a potent toxin which reaches the ventral horn cells of the spinal cord. There is hypertonus of the voluntary muscles usually accompanied by spasms

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Definition — Tetanus also known as lockjaw and trismus is an infectious disease resulting from contamination of wounds and raw surfaces with the *Clostridium tetani (Bacillus tetani)* and/or its spores The spores under approximate conditions proliferate or germinate giving rise to a potent toxin which reaches the ventral horn cells of the spinal cord There is hypertonus of the voluntary muscles usually accompanied by spasms

and sometimes by convulsions This reaction may be local or the condition may spread and become general

Etiology

Etiological Organism

The organism responsible for the disease is the *Clostridium tetani* (*Bacillus tetani*) It is an anaerobic bacillus growing only on media and in tissues where there is decreased oxygen tension Such media and tissues are said to be in a reduced state and have a lowered Eh or oxidation-reduction potential

The strains of organisms belonging to *Cl tetani* are not especially clear cut either as regards morphology or other characteristics Possibly one half the organisms showing morphological and cultural characteristics which would place them in this group fail to produce the typical toxin On the other hand some organisms elaborating a characteristic toxin fail to show a typical morphology and motility In order to be identified accurately as a member of this species two of the following three conditions must be fulfilled (1) morphological, cultural and biochemical conformation to the classical type (2) agglutination in high titre to one of the already known type specific agglutinating sera, (3) production of toxin causing characteristic symptoms and especially neutralizable by tetanus antitoxin

The young vegetative form of the organism is a rod with rounded ends 0 3 to 0 6 micra in width and . to 100 micra or more in length The latter type of organism exists as filaments which later may segment In from 36 hours to 8 to 10 days depending on the strain and pH and Eh of the medium sporulation occurs in a few or many of the rods Spores form at the end of the organism as swellings which at first are ovoid but later become spherical giving a drum stick appearance On maturation of the spore the remnant of the rod loses its affinities for stains and undergoes degeneration The latter is slower for this species of anaerobe than for many others The organism is actively, but not violently motile due to peritrichously arranged spirilliform flagella There are numerous non motile variants To determine motility the organism usually is incubated for 6 or more hours in a broth culture medium contained in capillary tubes sealed at both ends and observed microscopically in these tubes

Since the organism is an anaerobe it does not as a rule proliferate on the surface of appropriate media unless the atmosphere is reduced to at

least 15 millimeters of oxygen. The optimum tension is 3 to 8 millimeters of oxygen. The ability to grow, however, depends to a large extent on the nature of the medium and whether the organisms grow on the surface or in the medium. For example, the tetanus organism will grow aerobically profusely beneath the surface in simple nutrient media containing a little sugar and sufficient agar to solidify, if the pH is brought to around 8.5 and the organisms mixed into the medium before its solidification. Growth occurs since alkalinization reduces the medium, lowers the Eh, which condition is maintained below the surface. In other words, a gradient of Eh is established from the surface downwards in the medium, the organisms establishing growth in the suitable Eh range. In a broth medium many substances can be added to the medium to aid in lowering the Eh, such as other bacteria, fresh tissue, meat particles, titanium bichloride, cysteine, thioglycollic acid, glucose, platinum black and cotton wool.

Some investigators claim that *Cl. tetani* can be converted from an anaerobe to an aerobe, but coincidentally there occurs loss of virulence and marked morphological variation. Such possible alteration is of considerable significance, since an organism non-toxic when grown under aerobic conditions might revert to a toxic organism if put under ideal anaerobic conditions. It is likewise of interest that *Cl. tetani* grows best at 37° C. and loses its ability to produce toxin and shows slower growth when grown at temperatures approaching those of soil, 20° to 22° C. Probably half the organisms in the soil are non-toxic variants. In broth medium an odor develops described variously as cheesy, burnt feathers, like horse manure. Toxin formation commences within 24 hours at body temperature, 37.5° C., and continues for 7 to 14 days, even after active growth of the organism apparently has ceased.

Tetanus bacilli have been divided into nine types by agglutination reactions. Types II, III, IV and V seem especially closely related. In general cross agglutinations are considerable. There is a thermolabile H or flagellar, probably specific antigen and a more stable O or somatic antigen. Agglutinins are produced readily in rabbits protected by antitoxin by the intravenous injection of young cultures rendered non-toxic by washing and by heating for one and one half hours at 65° C. Titres as high as 1:1,600 are obtained after three injections and higher after further injections. Most strains agglutinate quickly with formation of floccules. Non-motile strains of type IV are slower to agglutinate, 5 hours at 56° C., and form only a fine granular sediment. Type III is apt to show auto-agglutination. The types predominating in different countries vary. Type I predominates in France and America and V in England and China.

Vegetative forms of *Cl tetani* are as susceptible to noxious agents as bacteria generally Spores apparently vary in their resistance some withstanding 100° C for 20 to 30 seconds while others withstand boiling water for 2 to 3 hours Salt content and hydrogen ion concentration have an influence on the effective temperature It seems that simple boiling should not be relied on but autoclaving at 115° C for 15 to 20 minutes is efficient Of the antiseptics all of which are uncertain oxidants probably are best Two per cent hydrogen peroxide acts in 24 hours and 30 per cent in five minutes One half per cent iodine in potassium iodide solution acts in 80 minutes and 1 per cent iodine trichloride in 30 seconds Sunlight and air destroy the spores in 18 days but protected from these agents they survive indefinitely Viable spores have been recovered from splinters after 13 years

The spores of *Cl tetani* are widely distributed in nature Nicolaier in 1884 demonstrated them in 12 out of 18 samples of country and city soil collected in Germany Since then figures have varied from 10 per cent recovery in Maryland to 72 per cent recovery from certain grazing lands of England Recently Gilles isolated virulent organisms from 9 of 63 samples of street dust in Baltimore Recovery in general parallels fecal contamination by animals and human beings Some consider the intestinal tract of animals the natural habitat and carrier of the organism Ten Broeck and Bauer fed one hundred tetanus free guinea pigs with food heavily contaminated with tetanus spores At the end of four months during which time the animals were kept in sterilized cages given sterilized food and well washed vegetables 75 of the 95 survivors still eliminated tetanus spores the estimated total number of which far exceeded those originally ingested That the intestinal tract might prove suitable for proliferation is suggested since it has been reported as markedly anaerobic

On examining dung of human beings and animals the following percentage isolations have been obtained human beings 0 to 34 7 horses 15 to 30 cows 0 to 80 guinea pigs 33 sheep 27 dogs 46 rats 37 hens 20 Recovery of the organisms seems dependent on eating habits food eaten in human beings occupation and area inhabited It appears that the problem is a feces to mouth one About half the organisms isolated proved non virulent Soils enriched with manure have been called tetaniferous soils and battles fought on such soils or injuries received contaminated with such soils have shown a higher incidence of the disease

The characteristic symptoms of tetanus are entirely due to the powerful exotoxin neurotoxin produced by the organism in its growth at the site of lodgement in the body The organism produces at least two exotoxins tetanolysin and tetanospasmin Tetanolysin is a hemotoxin

capable of dissolving red cells possibly also destroying leucocytes of most mammalian species It is unstable destroyed by 50 C in 20 minutes deteriorates on oxidation in air but in this case can be restored by reducing substances sodium hydrosulphate and is neutralized by its antitoxin It is rendered inactive by lipids alcoholic extracts of normal serum ethereal extracts of red blood cells and liver extracts Apparently it is absorbed by the liver and various substances such as animal charcoal and kaolin It seems of little pathogenic importance but may because of its leucotoxic power further infection

Tetanospasmin stimulates formation of its own distinct antitoxin Its amount seems correlated with the pathogenicity of the strain There seems to be a reverse ratio between its amount and that of tetanolysin It is the second most potent toxin known botulism toxin coming first and 0 000 006 gm of a dried ammonium sulphate precipitate from the toxic growth filtrate as originally used by Rosenau and Anderson in the Hygienic Laboratory at Washington regularly kills a 350 gm guinea pig By dialysis this product has been considerably purified to the extent that 0 000 000 03 gm is fatal to a 15 gm white mouse If one could calculate weight for weight 0 000 13 gm would be fatal for a 150 pound man

Contributing Causes

Tetanus the disease may be considered to be due to synergistic etiology since for its production the organism needs a definite set of conditions This set of conditions furnishes nutrient to the organism at a reduced Eh or oxidation reduction potential Reduced Eh means that the amount of oxygen due to conditions present is reduced much below that of the atmosphere and to a tension at which an anaerobe such as the tetanus organism can grow Production of a reduced oxidation reduction potential is aided by (1) presence of an accompanying aerobe (2) death of tissue (3) presence of ionizable calcium (4) tissue necrotizing agents

Vaillard found that if tetanus cultures are heated to 65 or 67 C for half an hour to destroy vegetative bacilli and toxin the toxin free spores can be injected into guinea pigs in large numbers without giving rise to the disease The spores do not germinate and are taken up in 2 to 3 days by phagocytes If the spores however are protected by being wrapped in filter paper they germinate giving rise to the disease Likewise trauma and aerobic organisms at the site of injection aid in giving rise to the disease Tissue debilitants such as lactic acid saponin triethanolamine toxins of *Cl welchi* or *Cl septique* even when injected at another site from the spores give rise to the disease

Francis found that contributory agents if injected in the same site at the same time as the spores result in death of all of the animals if injected 9 to 30 days after the spores 11 of 24 animals and if injected 30 to 90 days after the spores 2 of 20 animals Findings comparable to this for animals occur in wounds of humans Tulloch examining wounds of 100 soldiers without the disease found the tetanus bacillus 19 times Observation showed that tetanus might not occur for weeks or months after the wound had healed and then develop suddenly perhaps after operation on another part of the body

Bullock and Cramer found that injection of small quantities of ionizable calcium with toxin free spores gives rise to the disease in the guinea pig and mouse With washed bacilli but not with spores ionizable calcium can be injected into different sites at the same time or into the same site at a different time and the disease will result Soil shows much the same action as calcium Ionized calcium seems essential since calcium rendered un ionized by sodium carbonate fails to produce similar results In the first part of World War I it was observed that fighting in the highly cultivated fields of Flanders resulted in more tetanus than did battles on waste soil The highly cultivated soil contained an abundance of ionizable calcium

Fildes and colleagues emphasized the importance of low oxidation reduction potential Eh and showed that tissue necrosis whether by injury calcium or other organisms produces this effect Working with guinea pigs they found the potential of uninjured tissues too high to produce the disease On lowering the percentage of oxygen in the atmosphere from 21 per cent normal to 7 per cent however they were able to produce the disease in the presence of the mild contributory factor aleuronat or even sterile agar Contributory factors together with toxin production play their part in determining incubation period and severity of the disease

Prevalence

Tetanus is world wide Its prevalence varies in active military forces and in the civilian population Since the extended use of antitoxin prophylactically begun about 1915 and prompt and efficient debridement the mortality of tetanus in the armed forces has decreased out of proportion to that in civilian life At the present time because of almost universal toxoid immunization in armed forces and its lack of use in the civilian population one may expect fewer cases in armed forces much less severe tetanus when it does occur and a decreased mortality as compared with civilian life

Long and Sartwell reported 12 cases of tetanus among Army personnel in World War II 5 of which were fatal and of these individuals had received full prophylactic immunization and an emergency stimulating dose after injury Hall reported only one nonfatal case of tetanus among Navy personnel for the same period It is probable that rare cases of tetanus will occur among fully immunized individuals since there are a few who seem unable to respond by the production of antibodies Even the disease itself may fail to immunize completely as illustrated in 6 instances of second attacks recorded by Vener and Bower Decline of tetanus in the civilian population is attributable to improvements in surgery increasing use of antitoxin active immunization of children large number of Army and Navy veterans and education Since 1939 statistical study of tetanus is difficult since it is not listed as such However the 1936 1938 statistics indicate that deaths from tetanus are twenty times higher in the civilian population than in the U S Army 2 4 times higher among males than females 3 4 times higher among non whites than whites and higher in older and younger age groups especially in infancy Decline in the U S Army is shown in the following statistics of Long and Sartwell World War I 13 4 cases per 100 000 wounds and injuries 19 0-1941 (Incl) 4 per 100 000 and World War II (1942-1945) 0 44 cases per 100 000

In years past tetanus has been a horror of war and has indexed the efficiency of prophylactic procedures The danger is greater in fertilized d mp soil and as the tropics are approached Incidence in several wars has been as follows Crimean war (1854 56) of 12 094 wounded 0 75 cases per 1 000 (British) Civil war (1861 65) of 4617 wounded 2 07 per 1 000 Franco Prussian war (1870 71) of 95 000 wounded 3 5 per 1 000 Russo-Turkish war (1877) of 51 700 wounded 1 per 1 000 (Russians) World War I (before antitoxin) of 7 677 wounded 6 per 1 000 (Germans) (after antitoxin) of 380 000 wounded 0 8 per 1 000 (British)

The use of antitoxin reached appreciable proportions in the English Army in October 1914 and increased from then on Its prophylactic use resulted in (1) decrease in incidence in the wounded (2) increase in the incubation period (3) decrease in case mortality From 1914 to 1915 the average incubation period was 12 4 days and from December 1917 to April 1918 46 days Simultaneously the case mortality was reduced from 85 per cent to 44 3 per cent At first 500 units and later 1 500 units of antitoxin repeated weekly until the wound was healed were given

It was realized soon that adequate debridement was essential if the antitoxin was to serve its purpose and both tetanus and gas infections be largely eliminated Necessity of prophylactic immunization before operations for removal of foreign bodies became apparent because of such observations as those of Starker He collected 18 cases of tetanus from the literature in which the disease developed more than 60 days after receipt of the wound

Francis found that contributory agents if injected in the same site at the same time as the spores result in death of all of the animals if injected 9 to 30 days after the spores 11 of 24 animals and if injected 30 to 90 days after the spores 2 of 20 animals Findings comparable to this for animals occur in wounds of humans Tulloch examining wounds of 100 soldiers without the disease found the tetanus bacillus 19 times Observation showed that tetanus might not occur for weeks or months after the wound had healed and then develop suddenly perhaps after operation on another part of the body

Bullock and Cramer found that injection of small quantities of ionizable calcium with toxin free spores gives rise to the disease in the guinea pig and mouse With washed bacilli but not with spores ionizable calcium can be injected into different sites at the same time or into the same site at a different time and the disease will result Soil shows much the same action as calcium Ionized calcium seems essential since calcium rendered un ionized by sodium carbonate fails to produce similar results In the first part of World War I it was observed that fighting in the highly cultivated fields of Flanders resulted in more tetanus than did battles on waste soil The highly cultivated soil contained an abundance of ionizable calcium

Fildes and colleagues emphasized the importance of low oxidation reduction potential Eh and showed that tissue necrosis whether by injury calcium or other organisms produces this effect Working with guinea pigs they found the potential of uninjured tissues too high to produce the disease On lowering the percentage of oxygen in the atmosphere from 21 per cent normal to 7 per cent however they were able to produce the disease in the presence of the mild contributory factor aleuronat or even sterile agar Contributory factors together with toxin production play their part in determining incubation period and severity of the disease

Prevalence

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neonatorum occurred from contamination of the cord and circumcisions as practised by Jews and Mohammedans Even in 1909 30 7 per cent of the cases of tetanus were under one year of age It is obvious from the above figures that in tetanus neonatorum the basis of the disease was filth With emphasis on and education in cleanliness and asepsis and adequate debridement of wounds tetanus neonatorum largely has disappeared

In the last 0 years figures in the United States have shown a slight decrease in reported cases in 19 0 1 472 cases against 930 in 19 8 The states show some variation in rate As examples while the rate for Minnesota was 1 2 per 100 000 in 19 0 and 0 7 in 1940 that for Georgia was 8 and 1 5 respectively but in Georgia the rate in the white race did not vary much from the rate in Minnesota Higher incidence in the colored race raised the figures for Georgia the negro incidence being on an average 2 to 3 times that of the white It has been reported that in early years New York and adjacent states had an especially high rate supposedly because of a tetaniferous soil usually highly cultivated but in 19 0 the rate was 0 7 and in 1940 0 1 The decrease might suggest a more adequate educational system more adequate medical treatment or a soil which was less dangerous Lack of adequate attention cleanliness and lack of realization of the danger must be factors in the increased rate in negroes

Most cases of tetanus occur in July the cases in some areas being more prevalent when the ground is moist and when out of door life is at its height The majority of cases in most series where tetanus neonatorum is not a factor seems to occur in the scuffling ages between 7 to 16 with more cases in the age group between 1 and 6 than in the age groups after 16 Usually about three times as many males suffer from the disease as females which may be due to greater number of injuries in males However even in tears from childbirth tetanus does not seem to occur although the wound is in an area of easy contamination with tetanus spores

At one time Fourth of July injuries especially from wads shot into the hand from toy pistols caused a considerable number of cases of tetanus Starting with 417 cases in 1903 by 1915 there was a total of 1 119 cases of tetanus recorded for the United States 889 from blank cartridges Some fifteen years ago one of the authors observed three cases of tetanus none of which had been given antitoxin Four other cases observed on this Fourth of July who were given antitoxin did not develop the disease This experience emphasizes the danger of lack of attention to Fourth of July accidents when much of the material may be laden with tetanus spores and the matrix especially pistol wads may serve as an ideal contributory factor in the development of the disease Of recent years either none or one or two cases of tetanus due to Fourth of July accidents have been reported and in these instances the injuries have been of a more severe type This indicates the result of laws to control and to educate the public and medical profession

and usually after a secondary operation It has been observed that recurrent tetanus can occur from massage or manipulation of a wounded part In one case symptoms occurred 5 times in 15 months and in another that of a 12 year old boy there was more or less constant spasm for 2 years

Postoperative tetanus is an important problem Present day methods of control and processing of American made catgut are almost foolproof However Bunch and Quattlebaum find that substandard equipment and faulty sterilization can be repeatedly implicated in cases of postoperative tetanus and so advise postoperative prophylaxis

Referring to the unimmunized since antitoxin remains in the body about two weeks its reinforcement is necessary where the wound remains unhealed Both passive and active immunizing agents antitoxin and toxoid are best given coincidentally Operations on the very susceptible horse routinely should be accompanied with prophylactic immunization where previous active immunization with toxoid has not been carried out Possibly some individuals are more susceptible or have less sensitive or efficient antibody producing mechanisms to tetanus antigen than others

The question of how much antitoxin to give in prophylaxis for reduction of prevalence of tetanus has led to considerable discussion Figuring by weight that a unit of antitoxin is 10 times the least amount necessary to save the life of a 350 gram guinea pig for 96 hours against the official test dose of standard toxin (test dose is 100 minimal lethal doses) a man weighing 70 kilograms 154 pounds should require 20 units However since man is one of the most susceptible animals (horses are more susceptible and negroes are more susceptible than whites) and toxin production in the wound may be great larger doses 1 500 units are deemed necessary These should be repeated at intervals of a week or less until the wound is healed since all of the antitoxin may be eliminated from the body in 10 to 12 days

Tetanus in the civilian population is an entirely different problem from that in the military population in that the former is an uncontrolled group While a splinter probably would be immediately removed and the area treated in an army camp and prophylactic and/or active immunization given it might be neglected in a civilian population This holds for other types of injury While tetanus has been described in ancient literature its part in the mortality although not recorded appears to have been far greater in the civilian population than in armies at that time

In Charleston in 1856 tetanus accounted for 4 0 per cent of deaths and in New Orleans 3 7 per cent It is claimed that during this period one fourth of the children born in Rio de Janeiro died of the disease as compared to one half in British Guiana In our southern states it was of such concern that the plantation mistress visited often the negro hut to dress the child

In such hospitals as the Dublin Rotunda from 1757 to 1782 of 17 650 births it was reported that 16 per cent died of tetanus neonatorum Tetanus

and no one method can be decided upon because supposed repetition of a method of treatment giving good results in one series may show only mediocre results in another

Tetanus is more common and severe in the tropics In this country the highest rates are for cities of 2 500 to 10 000 population and lowest for rural areas As a rule southern states show a higher incidence in some apparently due to increased incidence in negro population 1 death in 300 to 400 while northern coastal states show the lowest incidence Whites show a higher mortality in Florida Louisiana and Texas suggesting influence of a subtropical climate The southern negro rates seem decreasing more rapidly than the white possibly due to increasing education of the negro in sanitation Damp soil and all year sports possibly help increase mortality

It must be realized that there is danger of contamination of anti smallpox vaccinations until healed but control of biologicals sold insures against contamination of the vaccine with tetanus bacilli and modern methods of vaccination have decreased chances of infection to almost nil The erroneous opinion held by some that tetanus does not occur with injury at the seashore must be discarded A splinter implanted under the skin is dangerous regardless of source One of the cases of our series resulted from a foot bruised at the beach

The few reports of series of cases that show a lower mortality with incubation periods under 5 days than those over 5 days are hard to explain Fatality probably depends on the amount of toxin entering the blood stream when and how it enters and when and how it reaches the nervous tissue

Variation of mortality in different series under different treatments is confusing some reporting as high as or higher than 60 per cent while other figures are as low as 27 to 29 per cent These variations depend on many variable factors in reported group of cases that make direct comparisons not valid as concerns methods of treatment It seems evident to us that good nursing care and intelligent therapy are important but it seems unjustifiable to say more

The outlook for reduction of mortality in tetanus seems to rest with prophylaxis by immunization of the population with tetanus toxoid and at least until it has proven valueless the administration of toxoid in conjunction with antitoxin in the treatment of the unimmunized case The fact that the tetanus death rate is low 0 4 per 100 000 seems no reason for failure in the future to immunize all children with combined diphtheria and tetanus toxoids While the reduction in mortality from 2 per 1 000 in the Civil War to 2 per 10 000 in World War I speaks well

Various workers Ten Broeck and Bauer have reported tetanus antitoxin in human beings who have not been immunized nor had the disease However others have failed to confirm this An average of 0 to 35 per cent of persons have tetanus bacilli in their intestines and some have felt that this might possibly be a source of stimulation of the immunity producing mechanism

Comparatively few who are injured develop tetanus However the custom of some large hospitals of omitting antitoxin where indicated because of infrequency of the disease and the danger of allergic reaction and neuritis from the antitoxin, seems an unwarranted gamble

Mortality

In 1940 in the United States there were 560 deaths from tetanus a rate of 0 4 per 100 000 In civil life the largest incidence is between the ages of 10 and 15 Even before the advent of antitoxin there was considerable variation in the stated percentage mortality Some workers gave a mortality of 90 per cent and some of 60 per cent or even less The type of case is of importance statistics including a large number of cases of tetanus neonatorum necessarily would show a higher mortality

If the incubation period is less than 6 days and no prophylactic antitoxin has been administered one may expect according to most reports a mortality as high as 90 per cent while if the incubation period is over 10 days a mortality rate of 50 per cent or less is more likely Huntington Thompson and Gordon reviewing 642 case histories found a mortality of 65 3 per cent in those not receiving treatment in those receiving less than 10 000 units of antitoxin of 58 6 per cent and in those receiving more than 10 000 units a mortality of 66 1 per cent These figures seem to indicate that larger doses of antitoxin are accompanied by high mortality rate, obviously other factors are not taken into account such as the larger doses having been used in patients seemingly sicker These authors bearing out what has been just stated decided that the length of the incubation period and duration of symptoms prior to admission were important in prognosis as did Hippocrates some 2 500 years previously Their statistics are interesting since in the early part of this century such workers as Vallas who analyzed 373 cases felt that antitoxin had reduced the mortality from 70 to 90 per cent to about 39 per cent Today just how great benefit is obtained from antitoxin treatment still is a question since some reports give mortalities comparable to Vallas for certain methods of antitoxin treatment while other reports are more like those of Huntington Thompson and Gordon The question of treatment and mortality remains unsolved

system by the blood lymph system direct blocking of peripheral nerves as advised by von Behring has no rational basis Their experiments on animals indicate that antitoxin has no therapeutic effect once a lethal amount of toxin has been fixed by body tissues and the period of incubation of fixation has passed However since the amount of fixation can not be determined active treatment with antitoxin is advised

In 1935 members of Abel s group began an investigation of toxin injected into the spinal cord They showed as Zupnik had suggested that spinal injections can produce tactile reflex motor tetanus without inducing any sign of muscular rigidity They found repeating Meyer and Frohlich s experiments that the lethal amount of toxin injected into any one dog s cord nonvital center was very much smaller $\frac{1}{4}$ to $\frac{1}{130}$ than the amount required to kill the animal when the toxin was injected intravenously subcutaneously or intramuscularly In all experiments the dog died within the week the time required suggesting that tetanus toxin may be altered when in contact with the cells of the spinal cord Abel and Chalian further showed that fixed toxin can be neutralized by antitoxin up to a certain point in the period of incubation While antitoxin mixed with toxin before injection results in protection an animal can die of tetanus with antitoxin in the blood stream A unit of antitoxin has 1 5 to 9 times the protecting power against toxin if these are mixed in vitro than when they are injected by intravenous route simultaneously but separately Antitoxin is only very slightly effectual against toxin placed in the spinal cord but very much more effective against toxin given intradermally intramuscularly subcutaneously and still more effective against that given intravenously

In animal experiments the incubation and survival period vary inversely with the amount of toxin The delay following cutting the cord above injection seems related to injury produced Injection into the medulla shows a shorter period while there are silent areas of the brain which if injected show no effect Rigidity or spasm of muscles of respiration is not observed following medullary injection the toxin apparently serving as a respiratory depressant as do certain drugs Terminal hyperpyrexia is frequent in dogs but does not occur in cats Injections of the lumbar cord produce tactile motor tetanus of hind limbs and of the cervical segment of the forelimbs Smaller doses are required in injections into the medulla These doses a fraction of the minimum lethal dose when injected into organs other than the central nervous system do not prove fatal Even when the antitoxin is given before the toxin relatively large amounts of antitoxin are required to save life or prevent symptoms This is especially true of injections into the medulla

for prophylactic immunization there is little reason for a rate as high as the latter with the advent of toxoid Prevention of tetanus seems to depend on active immunization in childhood and giving one dose of toxoid at the time of injury

Pathogenesis

While tetanus toxin except in tremendous doses is innocuous by mouth parenterally it has proved to be the second most potent bacterial toxin The mode of its absorption has been a cause of much contention Marie in 1897 found that toxin injected into the limb produced the disease only if the peripheral nerves were intact Shortly after that experimentation suggested that tetanus toxin injected into the limb is absorbed chiefly by motor nerve endings from which it passes up the axis cylinders to the anterior horn cells when symptoms occur The length of time taken for this passage accounts for the incubation period A small amount of toxin was thought probably to be absorbed by the lymphatics and carried by the blood stream from whence it is taken up by motor nerve endings in various parts of the body Meyer and Ransom emphasized dosage considering that a larger dosage more likely would be disseminated by the blood stream and lead to a generalized tetanus Severe and infected wounds are considered more dangerous because of likelihood of greater toxin production This of course does not hold in cases where severe tetanus occurs without identifiable wound or with only a slight wound

In 1903 Tiberti reported experiments to show that tetanus toxin injected subcutaneously passes into the lymph vessels and thence into the blood a small portion being absorbed by nerve endings and transmitted by the nerves to the nerve centers

Abel Lamont Shumacker Firor and colleagues (1935–1940) have considered tetanus a disease of dual manifestations (1) stiffness or rigidity of muscles due to direct action of toxin upon peripheral nerve organs in muscle tissue and (2) reflex spasms due to the action of toxin on the motor nerve cells of the central nervous system Local tetanus is considered to be due to local spread of toxin to muscles or groups of contiguous muscles with stiffness from poisoning of nerve end organs while diffuse distribution of toxin by blood stream to end organs of many voluntary muscles leads to general tetanus These workers consider the convulsive manifestations and death in most cases due to deposition of blood borne toxin in the central nervous system They maintain that since toxin is distributed through the body and into the central nervous

have been observed Congestion of the nerve centers of the medulla and cord resulting in inflammation and softening is noted commonly Peri vascular exudations and granular changes in nerve centers are observed When there is general congestion of the grey matter of the spinal cord and medulla there may be irregular patches of more marked congestion especially in the medulla and pons There may be minute hemorrhages in the congested areas

The motor ganglion cells may show degenerative changes and hemorrhages due to injury and rupture of the blood vessels during the violent spasms may be found in the muscles and elsewhere

In experiments on dogs Claude Putnam McKenna and Evans by injecting minimal lethal doses of tetanus toxin produced extensive foci of demyelinization of limited areas somewhat like those seen in multiple sclerosis This was associated with round cell infiltration proliferation of fixed glia and preservation of axones In human beings such changes are meagre Ganglion cells especially in the anterior horn may show swelling of cell body chromatolysis vacuolization and displacement of nucleus The changes in the human being are nonspecific and a matter of degree Those described for the nervous system are often cadaveric or agonal

Portal of Entry

In years past tetanus was classed as traumatic and idiopathic Today all tetanus is considered traumatic even though a portal of entry can not be found Therefore traumatic must be interpreted broadly For example Bruce showed that conditions such as trench foot might serve in harboring the organism Likewise there have been in the past numerous cases of vaccination tetanus in many instances traced to the shield used for protection Apparently tetanus neonatorum with incubation period of 6 to 12 days may result from contamination at cutting of the umbilical cord or of the raw surface afterwards The same holds for circumcision wounds and other wounds where there is soilage especially those following certain rectal genitourinary or gynecological operations Portal of entry through insect bites the respiratory tract and the gastrointestinal tract while probably less usual must be considered as possible An inflammation due to any microorganisms or inhalation of irritant gases may serve to allow entry of the tetanus organisms because of the raw surface produced

The frequency of usual portals of entry as tabulated by Anders and Morgan in 1905 and 1906 probably holds today Of 863 cases the atria

Recent work of the Abel school with parabiotic animals suggests that a lethal agent is produced which is not neutralizable by antitoxin and this may explain why antitoxin for results must reach the toxin before it has been fixed to nervous tissues Such an agent was postulated originally in 1899 by Courmont and Doyon and may help to explain the comparative ineffectiveness of antitoxin in treatment

It is interesting that monkeys actively immunized with toxoid injected into the blood stream have little protection to toxin injected into the cord but adequate protection to that injected intravenously

Demonstration of the two cardinal manifestations of tetanus by Abel and colleagues are interesting because of possible prototypes in clinical tetanus Varying degrees of reflex motor tetanus without muscular rigidity can be produced in animals by injecting the anterior horn of the cord with small doses of toxin The extent and severity of this manifestation will depend on dosage Injections into multiple muscular sites of minute doses as little as $\frac{1}{2000}$ of a minimal lethal dose may render the limb of the dog rigid for as long as three months In the dog after $\frac{1}{10}$ lethal dose has been injected into the brain the first symptom that is noticeable is difficulty in swallowing soon followed by chronic spasms of the pharyngeal muscles when the dog attempts to eat Later the spasms occur spontaneously simulating hydrophobia The spasms are not painful and between them the animal remains quiet In no instance is there evidence of involvement of muscles of trunk or limbs Such animals die in 24 hours with $\frac{1}{100}$ lethal dose they die in 17 days Even injections of toxin into the medulla requires an incubation period of 7 hours to 5 days

PATHOLOGY

In tetanus the wound often shows suppuration hyperemia and more or less hemorrhagic extravasation The nerve leading from the wound may be the seat of acute inflammation The wound when present may appear entirely healed While the nerves leading from the wound may show an acute neuritis this probably is due to sepsis and not to the toxin The fact that dirt clothing splinters manure frequently are the contributory factors present in the wound may well account for the pathological changes

The changes in the nervous system are no more characteristic than in the local wound In acute cases density of the cerebral tissue is increased and the grey substance is distinctly hyperemic In the chronic form the brain and meninges may be edematous and minute hemorrhages

The effects of administered antitoxin on symptomatology may be many ranging from allergy and anaphylactic manifestations to paralysis of cranial nerves The exact mechanism producing cranial nerve paralysis is unknown Some have tried to link it with the tetanus toxin

Incubation Period

Bruce in an analysis of 1 000 cases of tetanus found clinical incubation periods ranging from 2 days to 1 year i e the time between infection and onset of symptoms He found that in the first year of World War I 47 per cent of cases had short incubation periods and in the subsequent years after introduction of prophylactic immunization this was reduced to 10 per cent This finding correlated with the decrease in mortality from 58 4 per cent in 1914–1915 to 19 per cent in 1916–1917

Of Bruce's cases 896 were general tetanus and 99 local tetanus The incubation period of the average case was 9 days Of his series only 8 8 per cent had an incubation period of 7 days or less His group showed a somewhat smaller number in the shorter incubation period than groups of many others some series showing 25 to 45 per cent with an incubation period in the first week Short incubation periods were frequent in earlier years when many cases of tetanus neonatorum were included in the series Since as a rule the larger the number of cases with incubation periods in the first week the higher the mortality interpretations should be made with this in mind In future years there probably will be a shift of cases to longer incubation periods because of increased use both of prophylactic immunization and active immunization with toxoid

The true incubation period would be taken as the time from the initiation of the production of toxin to the onset of symptoms of the disease Confusion has arisen in this regard since frequently organisms lie dormant and begin to proliferate and form toxin after a variable period of time The organisms may lie buried in a scar and on injury the necessary accessory factors may become available initiating growth of organisms with production of toxin Accounting for these factors true in contradistinction to clinical incubation periods should fall within 1 to 21 days or an even narrower range 1 to 4 days in animals dependent on amount potency and rapidity of liberation of toxin from the site involved

Persons who have had recent i e within 4 weeks prophylactic inoculations usually have longer incubation periods because some of the toxin may be neutralized reducing the dose In tetanus from injured old scars severity may depend on immunity production from toxin absorbed from the site over the period of its existence This may range from none to

were arms and hands 291 feet alone 280 cephalic tetanus 53 The possibility of danger of tetanus must never be overlooked where there is a break in the skin Extraction of teeth childbirth (puerperal tetanus) picking the nose mucous membrane ulcerations etc may be portals of entry Bakay and Klimko in a study of 1 362 cases of tetanus in Hungary found these portals of entry puncture wounds 499 crushes 305 infection of umbilical cord 44 compound fractures 21 subinguinal hematomas 10 Splinters nails pins needles and superficial hemorrhage such as subinguinal hematomas are dangerous tools of the organism Burns frost bites trench foot hypodermic injections especially of quinine salts (tetanus rare in morphine addicts) cat gut and probably insufficiently sterilized gauze all have contributed to cases of tetanus The terminology in the older literature of outbreaks and epidemics of tetanus was a misnomer since the large number of cases occurring in an area was easily explainable on filth and lack of aseptic technique relative to wounds and raw surfaces

Symptomatology

The symptoms of tetanus are traceable to one of the organism toxins tetanospasmin the other tetanolysin has as a rule little if any effect The specific symptom complex is due to effect on nervous tissues Other symptoms frequently are added to these but they are due to factors such as other infection extent and site of injury and general condition of the patient There is experimental evidence that such other factors may modify the effects of tetanospasmin Various organisms and substances inoculated with the specific organism modify the severity and extent of the tetanus possibly because of modification of extent of absorption of toxin inactivation of toxin stimulation or inhibition of growth of tetanus organism

Certain findings in tetanus seem unrelated to the toxin itself Change in white blood count may or may not be present What variation occurs probably is explainable on the basis of injury suffered other infection present exertion from the disease administration of serum and sensitivity of hemopoietic system or is a characteristic of the individual The nervous manifestations other than those characteristic of the disease seem explainable on other diseased conditions and on the basis of the stability of this system in various stresses Fever may vary due to conditions as cited above A moderate degree of fever might be expected from the physical strain incident to the disease Possibly 10 per cent of the cases show a hyperpyrexia which often is terminal

TABLE I

Prodromes	*Duration in Days*	*Number of Cases*
Spastic Muscle Manifestations		
Stiff tongue	1	43
Stiff jaw	1 to 6	0
Stiff jaw	0	1
Stiff neck	1 to 4	8
Torticollis	19	1
Grimaces	2 to 3	
Dysphagia	1 to 4	6
Stiff shoulders	5	1
Stiff arm	1 4	
Stiff leg	3 t	4
Stiff back	1 to 4	2
Tense abdomen	1	1
Spasms injured leg	2	1
General convulsion	3	1
Epileptiform convulsions	7	1
Facial paralysis	1	
Pain due to Muscle Spasticity		
Sore jaws	1 to 5	1
Sore neck	2	
Sore shoulders	5	1
Sore knee	4	1
Back pain	1 to 6	4
Cramps in shoulder back and neck	1 to 5	3
Tender abdomen	2	
Intermittent chest pain increased on breathing	4	1
General Symptoms		
General aching	1 to 6	2
General weakness	3	1
Discomfort in eyes	1	1
Anorexia	1 t	
Slight fever		1
Malaise like grippe	to 4	
Sweating	2 to 6	2
Restlessness		1

localized less virulent type would be expected If symptoms occur at all, the tendency would be toward a localized tetanus

Prodromal symptoms due to tetanospasmin and upon which early diagnosis often is hinged include

1 Unusual muscle tension causing contracture in the region of the

considerable dependent upon whether the organism produced toxin which was absorbed It is not unusual to obtain a history of slight muscle tautness around a wound after injury or even a slight stiffness of the jaws which except for injury would not have been recalled While in many instances such a history may bear no relationship to the problem at hand in others there may well have been a subclinical toxin production and a slight antigenic stimulus to antibody production

Frequently it is stated that the clinical incubation period depends upon the time needed for the spores to germinate produce a symptomatic dosage of toxin and the time necessary for the toxin to reach the nervous system The true incubation period would be the time between the contact with the bacillus and the onset of the disease

The longer incubation periods before the production of tetanus in some cases suggests the possibility of previous exposure to organisms and their toxins in subclinical doses but in quantities sufficient to stimulate the antibody producing mechanism From our knowledge of the results of toxoid immunization this seems a logical assumption and may explain why many injuries which must be contaminated with dirt and tetanus spores never result in the disease Furthermore the long incubation period of some cases suggests the feasibility of giving toxoid with antitoxin in prophylaxis in the hope that antigenic stimulus may be sufficient to activate antibody production

Prodromal Symptoms

There are prodromal and classical symptoms The classical symptoms may occur without preceding prodromes and there is evidence that the prodromes may occur as shown in those receiving prophylactic immunization without the subsequent development of classical symptoms

Prodromes are those precursors of the classical disease symptomatology which allow the physician to anticipate the possibility or probability of the diagnosis The frequency with which prodromes are noted depends largely on how carefully the attending physician observes the patients Since prompt diagnosis leads to a greater recovery rate the importance of recognition of prodromes is evident at once

Prodromes may be divided into those due to the active toxin of *Cl tetani* tetanospasmin and those due at least partly to other factors previously discussed Table I lists prodromes in 61 cases

The prodromes given in Table I are to be anticipated in non immunized heterogeneous groups such as occur in a general civilian population With prophylactic immunization modification of symptoms to a more

3 Constipation This may be partly psychic It probably is not due to action on muscles of the gut Spasm of muscles of back and abdominal wall may have an indirect effect Constipation is apt to be present after the disease is established

4 Headaches which may be violent These are not characteristic

5 Restlessness especially at night This symptom may be due to tautness and slight pain of muscles becoming spastic Nights of restlessness may alternate with nights of sleep

6 Sweating This is irregular Action on muscles of the sweat glands seems unproven

7 Increase in pulse rate This is to be expected as a prodrome where there is increasing muscular spasm

8 Retention of urine This may be psychic from fear that urination may provoke spasm

9 Distressing dreams even delirium

10 Incontinence of urine especially in children

There is a tendency for prodromal symptoms to increase in severity Where there has been prophylactic treatment or partial immunization there is more tendency for them to be prolonged Two criteria have been used in determining prognosis (1) length of incubation period (2) length of period of prodromes Very generally the prognosis is more favorable with increase in combined lengths of these or increase in length of either

Classical Symptoms

With increase in hypertonicity there is a transition from prodromes of tetanus to typical symptoms of the disease The muscle phenomena characterizing the symptomatology of tetanus are due to the hyperirritability of the reflex nerve centers from fixation of toxin to the nerve cells As the disease progresses the hypertonicity of the muscles increases until the spasm is persistent When reflex irritability becomes sufficient spasmodic contractures are superimposed

Tetanus usually is acute Rarely is it chronic or recurrent Depending on the character and extent of muscle involvement it may be divided into *local general* and *cephalic forms* Tetanus neonatorum would fall under the general form which is by far the more usual form In *local tetanus* only the muscle groups surrounding the wound are involved This type is unusual in man unless there has been passive partial or active immunization In the *general form* there is a somewhat generalized spasm although one area may be affected predominantly As a rule the jaws are involved In addition the more or less generalized condition fre

wound The necessity of observing for such signs in all wounded must be impressed upon physicians and nurses

2 Pain and spasm in muscles of face neck and of deglutition In a minor number of cases of tetanus there is no external injury making manifestations such as these of especial value

3 Exaggerated reflexes in involved muscles especially in the vicinity of the wound and in any group of muscles becoming spastic Tapping with the fingers frequently will demonstrate presence of increased reflexes

4 Pain on swallowing with an objectively negative throat Occasionally spasm of throat muscles may give rise to complaint of sore throat

The preceding symptoms (1 to 4) may occur several days before the onset of disease and show a tendency to increase in severity with time Unfortunately tetanus often is not considered by physicians as a possibility Probably 2 per cent of cases initially are treated by extraction of a tooth or palliatively for disease of the nose and throat

5 Pain in back with mild degree of stiffness Difficulty in walking usually increasing with time

6 Cramps in muscles especially near wound excited especially by external stimulus

7 Twitching of muscles with possibly tonic contraction especially on tapping with fingers

8 Tonic spasm of muscles especially flexors in wound area

9 Excessive yawning

10 Trembling tongue when protruded drawn to one side

11 Darting muscular pains

12 Restriction of lateral movement of mandible

The preceding prodromes may be brought out especially on fatigue and may lead to restlessness and shivering Because of fatigue and its association with long marches and exposure tetanus coming on under such conditions has been called war or fatigue tetanus It is important that the above signs not be dismissed as fatigue since this very condition may bring on tetanus and certainly aggravate the condition An individual in the best of health and rested is much better suited to cope with any infection or noxious agent including tetanus if not in too great concentration

There are various symptoms enumerated in the following headings (1 to 40) which may be present and considered non specific

1 Anxious expression on face This may be due to concern with reference to symptoms There may be slight spasm of muscles of the face

2 Frequent urination with pain This may be more psychic than due to the effect on muscles of urination

or trismu Measuring the amount of opening of the jaw at the incisors is one index of increasing or decreasing severity of the disease The degree of opening may be too slight to allow feeding and before the development of the nasal stomach tube extraction of teeth sometimes was necessary Rarely the spasm of the masseters becomes so great that the teeth and jaw are fractured

Tonic spasm not infrequently affects the muscles of deglutition resulting in dysphagia Spasm of the laryngeal muscles may be such that the varying resultant degrees of stenosis interferes with respiration at times necessitating tracheotomy Likewise spasm of the diaphragm may interfere with respiration and contribute in the causation of death The abdominal muscles may become rigid and lead with other symptoms to the erroneous diagnosis of an abdominal catastrophe

External stimuli such as optic acoustic visual thermal or tactile may provoke spasmodic contractures Hyperirritability often may be illustrated by contractures precipitated by a slight breeze or even a whisper The groups of muscles in spasm determine the position of the body Twenty six of our series assumed a position of opisthotonus More rarely positions of emprosthotonus and pleurosthotonus are assumed In opisthotonus the body is stiffened and bent backwards in emprosthotonus forward and in pleurosthotonus laterally If the force of assuming these positions is sufficient fracture and crushing of the vertebrae may occur

Another condition due to spasmodic contractures is that in which the forehead becomes wrinkled eyes fixed and the facial muscles drawn back the lips baring the teeth The result is a mocking grin known as *risus sardonicus* Well marked cyanosis and respiratory difficulty occur when spasmodic contracture fixes the diaphragm and intercostal muscles and produces spasmodic laryngeal stenosis If not relieved such a condition results in asphyxiation Asphyxia is due to spasmodic muscular stenosis and edema of the larynx or results from spasmodic contracture of the diaphragm and intercostal muscles Both conditions may occur simultaneously Recurring spasmodic contractures of the laryngeal muscles may give rise to symptoms resembling hydrophobia Any or all of the contractures occurring in tetanus may be painful

Acute general tetanus as a rule is accompanied by a rise usually slight in temperature and some rise in pulse rate depending on the condition of the patient Sweating usually is profuse and there may be varying amounts of cyanosis Slight leucocytosis is apt to be present Trismus lockjaw and risus sardonicus usually appear early but may be late in the disease The jaws become firmly fixed and the patient find difficulty in opening his mouth When trismus occurs the muscles of

quently has a site from which spread takes place such as the lower limbs in ascending tetanus and the upper extremities in descending tetanus *Cephalic tetanus* usually is considered that form in which there is paralysis of one or more of the cranial nerves Care must be taken not to confuse it with nerve involvements resultant from the administration of anti toxin

Much of the symptomatology of tetanus can be defined in terms of severity of the disease Either the individual possesses less or more acquired or tissue immunity the organisms elaborate more or less toxin or the wound or conditions are such that elaboration and absorption of toxin are great or little Thus an individual almost immediately de veloping generalized spasm with almost persistent contracture is one in whom susceptibility is great much toxin is formed or toxin absorption is great or all are present With reverse conditions development would be slowed and the condition not so acutely severe

Of 61 cases the muscle groups involved varied masseters in 59 abdominal muscles in 27 posterior cervicals in 26 spinal in 24 flexors of the legs in 6 and of the arms in 11 There were 2 cases which might be classed as cephalic tetanus

Many so called atypical cases of tetanus have been described After abdominal operations a splanchnic non generalized tetanus has occurred resulting in contractions of the muscles of deglutition and respiration with death Cephalic tetanus may show such divergent variations as the following (1) non paralytic with simple trismus and contracture of certain facial muscles dysphagic with involvement of the pharyngeal muscles or hydrophobic with violent convulsive spasms of the muscles of the face neck pharynx and diaphragm (2) paralytic with contracture of certain facial muscles (3) paralytic after trauma of eye or adjacent parts involving the motor nerves of the eyes especially the third but sometimes the fourth and sixth (4) paralytic of hypoglossal nerve with labio pharyngeal paralysis A unilateral tetanus has been described in which the symptoms predominate on one side of the body even during generalization of convulsions giving rise to pleurosthotonus In tetanus of the limbs there may be a monoplegic form with stiffness of one limb and slight transitory trismus probably better classified as local tetanus In other forms however possibly also best classified as local tetanus contractures of the upper limbs with hands held flexed superior para plegic or of the lower limbs with limbs in forced extension inferior para plegic may occur

Since spasm of the masseters locks the jaw to a variable degree and such spasm usually occurs in tetanus the disease has been called lockjaw

Besides the organisms may not show the typical appearance or may be present in small numbers and overlooked. Carbolfuchsin and Gram stain usually are used. The organisms are gram positive when they take the stain well.

For cultural examination cooked meat medium or blood agar and plain agar plates may be used for incubation anaerobically and over alkalinized nutrient agar medium or thioglycollic acid medium for incubation aerobically. After 72 hours incubation at 37 C, when spores are present in fluid or semi-solid media, heat the culture to 75° to 80 C for 30 minutes to kill any non-sporing organisms and reculture on blood agar plates anaerobically for isolation of pure colonies. Observe for motility. Pure cultures may be obtained also by inoculating the material into the water of condensation of an agar slant and then incubating the tube anaerobically in an upright position. The tetanus bacilli produce an effuse, tenacious, proteus-like growth over the surface of the slope. Subcultures from the edge of the fern-like growth usually result in a pure culture after several transfers. In a shorter method the material may be suspended in bouillon and kept anaerobically at incubator temperature for 24 to 48 hours, thus allowing the organism to multiply. All vegetative forms then can be destroyed by heating for 30 minutes at from 75 to 80° C. The bouillon can be inoculated on blood agar plates or other suitable medium and incubated anaerobically.

Some of the original material is emulsified in saline, or the heated culture is mixed with sterile emery dust, calcium chlorid, sterile splinters or pumice powder and injected subcutaneously into the thigh of an 8 to 10 ounce guinea pig. More satisfactory results are obtained with 0.5 c.c. of a ten day broth culture or its filtrate. A control animal protected by an intraperitoneal inoculation of 500 units of tetanus antitoxin should receive a similar injection at the same time. If virulent Cl. tetani are present, the unprotected animal will exhibit characteristic symptoms in 12 to 24 hours and die in 1 to 4 days. A white mouse can be used in place of the guinea pig, in which case the material is injected subcutaneously at the root of the tail and the animal observed for convulsions, first spasms of the leg, with death within 2 to 3 days. Similarly the spinal fluid of the acute case may be tested for toxin by inoculation of a mouse or guinea pig.

Differential Diagnosis

The following conditions may be confused with tetanus but usually can be differentiated.

the neck stand out like cords As the disease progresses involvement of the diaphragm and laryngeal muscles may occur There develops difficulty in swallowing and breathing

With general convulsions the diaphragm becomes fixed in inspiration the larynx contracts the patient becomes cyanotic and asphyxiation may occur Epigastric pain which has been diagnosed mistakenly as an abdominal catastrophe frequently is a forewarning of respiratory symptoms with poor prognosis Occasionally the case may show resemblances to hydrophobia or laryngeal stenosis from contractures and may demand tracheotomy

Death may result from pneumonia exhaustion asphyxia or spasm of the heart More rarely hyperpyrexia plays a rôle In our series of 20 deaths 11 died from asphyxia 1 from laryngeal spasm 1 from acute ascending tetanic convulsions and 9 from spasmodic contracture of the respiratory muscles Of the remainder 2 died during general spasmodic contractures 2 from pneumonia with mouth temperatures of 107° and 108° F One patient dying in spasms had a temperature of 106° F The duration of the disease in the 36 recovered cases varied from 4 to 34 days in 34 and in one it was 43 and in another 58 days

Diagnosis

Diagnosis of tetanus in its early stages sometimes is difficult The absence of a history or other evidence of a wound frequently confuses the physician The organisms frequently are hard to demonstrate and the prodromes often not sufficiently definite to arouse suspicion The classical symptoms however cannot be mistaken but since these frequently occur after some days of prodromes the benefit of treatment will be reduced proportionately The symptoms often show increase in intensity through the prodromal period These prodromal symptoms may not show for example as much persistence of muscle spasm as later so that typical criteria are not as dependable for differentiation

Laboratory Diagnosis

The bacteriological diagnosis is made on the finding of the organism This often is difficult and in the majority of cases probably would be unsuccessful The pus tissue scrapings or wound secretions are stained for morphologically typical organisms The characteristic drum stick spores of *Cl tetani* are looked for but this method is merely preliminary since they may be non virulent anaerobes having similar morphology

paralysis of cranial nerves sinusitis In *poliomyelitis* there may be marked trismus and a differential diagnosis may be difficult The high temperature and somewhat clouded mentality commonly present are unusual in tetanus Muscles twitching in *encephalitis* may suggest tetanus but there are also tremors and athetoid and choreiform movements Furthermore the characteristic lethargy of encephalitis of von Economo type is present in 80 per cent of cases and eye symptoms in about 40 per cent i e diplopia strabismus ptosis of the eyelids optic neuritis choked disc irregular pupils and photophobia Rarely in adults but more commonly in children a tense and painful abdomen due to muscle spasm may be the earliest indication of the onset of tetanus Such phenomena may suggest acute *surgical abdominal conditions* However the presence of a wound the character of the onset of the pain blood study the past medical history and the subsequent course readily allow the differential diagnosis to be made Examination of the blood for carboxyhemoglobin should differentiate *carbon monoxide poisoning* *Cranial nerve conditions* would tend to be more localized on one side while proper examination should make the diagnosis of sinusitis

Prophylaxis

Prophylaxis against tetanus consists of active or passive immunization or both and an efficient debridement Active immunization consists of administration subcutaneously or intramuscularly of 0 5 to 1 c c of plain or alum precipitated tetanus toxoid at 3 to 4 week intervals for three and two doses respectively Passive immunization consists of giving 1 500 units of antitoxin subcutaneously or intramuscularly at weekly intervals until the wound incurred is healed The debridement entails removal of all dead tissue thus removing appropriate sites for growth of the organism with generation of toxin

Active Immunization

Probably the first examples of production of active immunity by means of toxoid were the experiments of Behring and Kitasato in 1890 when they produced transitory immunity in rabbits with filtrates of cultures of the tetanus bacillus and 3 c c of 1 per cent solution of tetrachloride of iodine injected at the same point This was repeated every 24 hours for 5 days The tetrachloride of iodine probably acted to detoxify the toxin On injecting into a mouse 0 2 c c of the blood of rabbits thus immunized a certain degree of protection

Strychnine poisoning — History of use of the drug may be obtained Contractures begin with clonic spasms after short interim of tonic spasm are not persistent and the jaw and neck are not involved early if at all The temperature is normal objects look green there is more rapid onset the course is brief and the hands are affected often The drug may be recovered from the gastric contents and usually there is no history of a wound

Tetany — There are predisposing causes and the extremities are affected mainly with characteristic posture The spasms of tetany are bilateral and symmetrical with intermissions Tapping the facial nerve may result in spasm The clonic involvement of the hands fingers extended as far as the interphalangeal joints but flexed at the ends is quite characteristic The thumb is flexed and tucked inside the fingers Feet are semiflexed at the ankles and the toes strongly flexed Tetany occurs usually in children without history of wound Serum calcium and phosphorus quantitations should aid in differentiation

Trismus — This condition may be reflex from the teeth dental caries impacted wisdom tooth etc Vincent s angina tonsilitis osteo arthritis peritonsillar abscess serum sickness with edema of the throat dislocated mandible mumps Often it is unilateral and the characteristics of the condition make its nature evident

Rabies — Psychical disturbances such as hallucinations are present The features appear wilder there may be mania and there is fear of taking fluid The spasms are mostly of the larynx muscles of deglutition and respiration rather than the muscles of mastication Later the case shows stupor Certain instances of cephalic tetanus have led to confusion In rabies there is a history of bite of animal and usually a longer incubation period There are few cases of tetanus caused by animal bites

Meningitis — There is a stiff neck rather than jaw characteristic spinal fluid usually classical evidence of an infection rather than a nerve intoxication The sensorium is apt to be clouded fever usually is higher at least initially and the headache is more constant Lumbar puncture yields a characteristic fluid

Hysteria — Nervous wounded men with knowledge of symptoms of tetanus develop trismus Hysteria however should not be assumed without inquiry In our series a young woman known to be nervous developed tetanus which initially was diagnosed as hysteria In hysteria spasm is not persistent and is irregular

Other conditions which have been confused are poliomyelitis encephalitis acute surgical conditions in the abdomen carbon monoxide poisoning

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antitoxin could be demonstrated. Roux and Vaillard mixed tetanus toxin filtrate with decreasing amounts of iodine and injected this with the production of antitoxin. Roux stated that 35 minutes after injection of toxin into the abdominal cavity of a rabbit, antitoxin could be demonstrated. Behring later added iodine trichloride in diminishing concentrations, 0.25 to 0.15 per cent, to filtrates, inoculating this toxoided material. Other materials used for toxoiding were heat, Gram's solution and lactic acid. This work paved a way for the toxoid and antitoxin treatment of today.

The value of formaldehyde in converting toxin to toxoid, i.e., removing the toxin properties yet retaining the immunizing power, was based on the fundamental observations of Salkowski and Loewenstein and von Eisler. These authors observed that toxins treated with formaldehyde lose their toxic properties but retain their antigenic properties. The value of toxoid in active immunization to diphtheria was established by Ramon. In 1924 Ramon prepared tetanus toxoid by combined action of formaldehyde and heat, and since that time Ramon and colleagues and workers in other countries have corroborated the value of tetanus toxoid in active immunization against tetanus. Various preparations of toxoid have appeared, but the plain and alum precipitated toxoid are recommended at present. Ramon prepared a toxoid by adding 3 to 4 c.c. of 40 per cent solution of formaldehyde to 1 liter of tetanus toxin and then incubated the mixture at 37° C. for 3 to 4 weeks. There have been various modifications of this procedure, and in recent years an alum precipitated toxoid has been prepared.

At present the National Institute of Health permits the use of alum as high as 2 per cent. The alum precipitated toxoid is prepared from the usual formaldehyde treated toxoid. The use of alum is based on the work of Glenny, Pope, Waddington and Wallace in 1926, which showed that the antigenic value of diphtheria toxoid is considerably intensified if toxoid is precipitated with 0.1 per cent of potassium alum. The U. S. Government standard requires that one dose of alum precipitated toxoid injected into a guinea pig must produce, after an interval of 6 weeks, at least 2 units of tetanus antitoxin. Ramon and his coworkers titrated toxoid by means of the flocculation test and defined as 1 antigenic unit that quantity of toxoid which gives standard flocculation with 1 unit of antitoxin. Since the accuracy of these methods of titration are not accepted universally, the need of an acceptable method of standardization is evident.

It is probable that there will be further refinement in the tetanus toxoids at present on the market. The American products have given

considerable reactions These reactions apparently are due to the peptone used for culturing the organism A synthetic medium is beginning to be used now from which apparently there will be little reaction This probably will replace peptone media There is some evidence that a slight amount of reaction at the site of injection is desirable if immunity is to be produced

Apparently injection of toxoid or toxoid vaccination produces an immunity both to the toxin and the organism The amount of antitoxin in the serum of one who has received an injection does not necessarily go hand in hand with immunity as judged from animal experiments It has been estimated that 0 1 to 0 2 unit or more of antitoxin per c c protects against tetanus This does not take into account sensitivity of antibody producing mechanism or ability of tissues to react in this respect which probably is of considerable importance It seems that best results are obtained with an immunization extending over several months that women in physically good condition and younger individuals respond with greater antitoxin production and that the immunization may be permanent although the antitoxin titre becomes reduced in time Ramon writing in May 1939 stated that not a single example of tetanus had been known to occur in a person vaccinated with toxoid The fact that there are several reports of recurrence of tetanus leads to the doubt that the immunity can be absolute always

Ramon and Zoeller have reported a titre of antitoxin of 0 005 unit as long as 8 or 9 years after toxoid vaccination The French army has reduced tetanus in its horses which it has vaccinated with toxoid since 1925 to practically nil Ramon and Zoeller have found 0 004 to 0 3 units in 13 human beings 4 and 5 years after toxoid vaccination Ramon considers this unit age will afford immunity against tetanus spores A stimulatory dose in a patient vaccinated with toxoid it is agreed will cause a rapid rise in antibody titre to as much as 25 to 75 units per c c which is much higher than that obtained with prophylactic antitoxin

Booster or stimulatory doses subcutaneously or intramuscularly are advised on injury and on commencing hazardous undertakings if the individual has had adequate active immunization Active immunization with alum precipitated toxoid with 2 doses 3 to 6 months apart is advised Later booster doses can be given effectively by intranasal instillation according to Gold Results suggest that alum precipitated toxoid is better than plain toxoid

Vaccination for tetanus with toxoid has been compulsory in the French army since 1936 Not a case of the disease has occurred in the

1 500 000 vaccinated Active immunization was begun in the Russian army in 1937 in the Italian in 1938 and in our army in 1941 When the present war broke out in 1939 toxoid vaccination was voluntary in the British army but over 90 per cent of the British troops in the forward area were protected No cases of tetanus among toxoid vaccinated persons have been reported

Active immunization of all civilian population subjected to hazard is advised Apparently a better response is obtained when other vaccines such as typhoid and paratyphoid or diphtheria toxoid are combined with the tetanus toxoid The long interval between doses of toxoid 3 or more weeks should be maintained and this if anything affords better protective response generally Combined administration of tetanus toxoid and diphtheria toxoid to children is advocated as routine The reaction to the combined vaccine is slight if the toxoids are free of excess of foreign substances

At present plain toxoid is prepared by treating the toxin with 0 3 to 0 4 per cent formalin incubating at 37° C for several weeks then inoculating in 5 to 10 c c amounts into guinea pigs to be sure it is non toxic. Three doses of 1 1 5 and 1 5 c c at 3 week intervals usually results in 0 5 to 1 0 unit of antitoxin per c c of serum in individuals injected The maximum titre is reached in 3 to 5 months and the protection is considered as great as that from 1 500 units of antitoxic serum

The alum precipitated toxoid gives fewer reactions than the plain toxoid because of less foreign substance and because of slower absorption because of its higher antigenic activity it is preferred Two injections of 0 5 and 1 0 c c at 3 to 4 months interval give quicker antitoxin response than 3 doses of plain toxoid While the antitoxin titre decreases with time the booster dose is capable of stimulating it to an adequate protective value within the usual incubation period of tetanus Such booster doses tend to raise the immunity to the disease and in hazardous occupations annual reinforcement of immunity by booster doses may be advisable If the booster dose is given intranasally 0 1 c c alum precipitated toxoid into both nostrils for 3 successive days is advised

A scratch test for sensitivity to tetanus toxoid has been advised but such sensitivity is unusual possibly because of less exposure to proteins of the organism than to many others used for vaccines Adults are less sensitive to this toxoid than to diphtheria toxoid It is possible because of the long spacing of doses that a scratch test before doses following the first dose may prove desirable especially if the individual shows allergic tendencies If the test is positive small doses increasing at appropriate intervals as in a desensitization procedure should be resorted to

The United States Army requires vaccination with plain tetanus toxoid Three doses of 1 c c are given subcutaneously at not less than 3 or more than 4 weeks Stimulating doses of 1 c c are injected subcutaneously at the end of one year during the month prior to departure for theater of active warfare unless such departure takes place within 6 months after administration of stimulating doses if a burn or severe wound is incurred on the battlefield in a secondary operation with manipulation of an old wound when deemed advisable and on receipt of lacerated wound puncture wound powder burn or other condition which might be complicated by tetanus

Personnel of the United States Marine Corps and all Naval personnel are being given alum precipitated tetanus toxoid on the same day with other vaccinations when these are given Two doses of 1 c c are given *intramuscularly with an interval of 4 weeks between injections This is* the initial injection A single stimulating dose of 1 c c is given at the end of a year only Emergency vaccination of 1 c c is given when burn or *wound is incurred in secondary operations or manipulations of old* wounds when deemed advisable in puncture and lacerated wounds powder burns and other conditions which might be complicated by tetanus

Passive Immunization

The value of antitoxin in prophylactic immunization was shown in World War I and in civilian populations since that time When to give antitoxin and when not to is a problem which the medical man must decide There is little doubt of its advisability in puncture wounds gun shot wounds compound fractures penetrating wound Fourth of July accidents deep cuts and especially where dirt clothing splinters glass and other foreign bodies have been carried into the wound

The procedure in giving antitoxin must be modified when the case proves allergic Cases are first tested by intracutaneous injection of 0 1 c c of antitoxin diluted 1 to 10 with sterile saline if the history indicates sensitivity or if there is any doubt 1 to 100 dilution should be used If in twenty minutes a wheal with an area of redness around it has formed at the site of injection and especially if projections or pseudopods extend *from the wheal the test is positive If there is a history of hypersen*sitivity a simple scratch test may be safer In all cases a solution of epinephrin must be on hand to be used at once in case symptoms of shock appear Tests are done on an extremity so that a tourniquet can be applied proximally if there is a reaction Despite negative tests it is

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munity lessens with each injection Passive immunization with foreign antiserum usually lasts no longer than three weeks and there are instances where it has not been demonstrable after a week

The Army and Navy require antitoxin for those not protected by active immunization A practice of giving tetanus antitoxin and the first dose of tetanus toxoid simultaneously is followed by some This proves valuable in severe wounds and where tetanus spores become encysted in scar tissue The necessary subsequent doses of toxoid for the initial course of immunization should be given at the regular intervals prescribed Ramon and colleagues showed that toxoid given with antitoxin acted as a first dose in active immunization

A prophylactic injection of 1 500 units of antitoxin results in 0 1 to 0 25 units of antitoxin in the recipient's serum This titre is maintained only for 4 to 11 days The first dose of toxoid produces no detectable antitoxin but merely prepares the patient for subsequent injections This does not mean that no protection is afforded The toxin of the organism in the wound could well serve as a stimulus or second dose Two weeks after the second injection of toxoid nearly all patients show antitoxin in their blood in amounts supposed to afford adequate protection Thus even a first dose of toxoid aids the patient The amount of antitoxin 2 weeks *after the second injection might be expected to be of the order of* the unitage afforded by 1 500 units of antitoxin injected into the unimmunized individual To the third and subsequent injections there is an even quicker response in antitoxin production

Procedure Recommended for Prophylaxis

In prophylaxis in childhood three injections of 2 c c of combined diphtheria tetanus toxoid at three week intervals or two injections of 1 c c of combined alum precipitated diphtheria tetanus toxoid at an interval of three months are to be given preferably at 9 to 10 months of age The two toxoids also can be given at different times Later when subjected to the danger of tetanus booster or stimulatory doses of 1 c c of either type of toxoid are given for protection Military forces farmers stock raisers stablemen trench diggers construction workers truck drivers those about to have operations on the rectum and those subject to wounds with contamination by soil or feces are to be given active immunization with either three injections of 1 c c of plain toxoid at three to four weeks intervals or two injections of 1 c c of alum precipitated toxoid with an interval preferably of 3 to 4 months Alum precipitated toxoid gives a quicker response and preferably is to be given intramuscu

good practice to give 1 c c of the serum subcutaneously ½ to 1 hour before making an injection intravenously In some cases the reaction is so marked that it is advisable to seek serum from a different species of animal usually cow or goat If such is not available attempts to desensitize the patient should be made

Since there may be general sensitivity without skin sensitivity care always must be taken in giving antitoxin Usually in desensitization the initial dose of serum is 0 01 c c subcutaneously in an extremity with a tourniquet in place proximally so that it can be tightened readily at the first sign of serum reaction In extremely sensitive cases the first injection should be diluted 1 to 100 A preliminary injection of another extremity with 0 6 to 1 c c of 1 to 1 000 epinephrin usually will prevent the occurrence of possible anaphylactic shock If no unfavorable symptoms occur the dose may be doubled every thirty minutes until 1 c c of serum has been given subcutaneously Then thirty minutes later 0 1 c c of serum diluted with saline may be given intravenously

At intervals of 20 minutes thereafter the intravenous dose may be doubled until adequate serum has been given The amount given depends upon the reaction of the patient If the reaction is severe it may prove advisable to repeat a dose one or more times until the reaction is less severe and then proceed with a larger dose If injections are to be made intraspinally it is probably best to bring the intravenous tolerance to 10 c c and then inject the required amount with caution Injections should not be made into the same site if a number of days apart and should be made as often as every 5 to 7 days if the danger of local anaphylaxis Arthus phenomenon serum sickness or general shock is to be avoided The serum should be at body temperature and injected slowly the patient should be watched and a tourniquet and epinephrin solution should be at hand to be used in case of reaction

The prophylactic dosage for adults and children ordinarily is 1 500 units of refined concentrated antitoxin There is no variation in dosage in child and adult since the injury will generate toxin equally well in either case The antitoxin should be given to the unimmunized individual immediately after injury and *where possible 24 to 48 hours* before an operative procedure in which tetanus is a possible danger In an injury it is advisable to give it intramuscularly near the wound and around nerves if these are present in the wound In very severe wounds 3 000 to 10 000 units are to be given If several days have elapsed since injury antitoxin around the wound and intravenously is advisable Injections of 1,500 to 3 000 units should be given every 5 to 7 days with severe dirty wounds continued until healing has occurred Duration of passive im

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Procedure Recommended for Prophylaxis

In prophylaxis in childhood three injections of 2 c c of combined diphtheria tetanus toxoid at three week intervals or two injections of 1 c c of combined alum precipitated diphtheria tetanus toxoid at an interval of three months are to be given preferably at 9 to 10 months of age The two toxoids also can be given at different times Later when subjected to the danger of tetanus booster or stimulatory doses of 1 c c. of either type of toxoid are given for protection Military forces farmers stock raisers stablemen trench diggers construction workers truck drivers those about to have operations on the rectum and those subject to wounds with contamination by soil or feces are to be given active immunization with either three injections of 1 c c of plain toxoid at three to four weeks intervals or two injections of 1 c c of alum precipitated toxoid with an interval preferably of 3 to 4 months Alum precipitated toxoid gives a quicker response and preferably is to be given intramuscu

larly Booster or stimulatory doses are to be given a year or more after completion of the active immunization when the individual is or is about to be subject to the danger of tetanus Individuals with deep puncture or lacerated wounds wounds with contaminated foreign bodies or wounds apt to scab over necrotizing bruises severe frostbite compound fractures dirty wounds Fourth of July injuries induced abortions operations on scars or operations apt to be soiled with dirt or feces inflammatory lesions of the feet when working in trenches are among those to be given booster doses of toxoid if previously actively immunized or 1 500 to 6 000 units of antitoxin depending on the seriousness of the condition together with the first dose of toxoid if not previously actively immunized The antitoxin is to be repeated at intervals of a week or less as indicated by the condition and the toxoid is to be given as in the procedures for active immunization However the interval in toxoid adminstration may be shortened to one week if the seriousness of the condition indicates The amount of toxoids to be given depends upon the source of the material or the firm supplying it The directions on the package should be followed The quantity values we have given are examples of amounts used in preparations frequently used It is obvious from this discussion that the goal in active immunization against tetanus must be a completely protected population and that this is accomplished best by toxoid adminstration in the preschool years when reactions are less severe

Prognosis

If the incubation period is more than 7 days and the prodromal period more than 2 days the prognosis is considered good in an otherwise healthy individual Comparing the two the length of the period of onset is more important The length of this period often will determine whether the rigidity will become worse or pass off after reaching a certain peak Death usually occurs within 7 days Prognosis also depends on general health physique and age

Prognosis is grave in the very young and those over 60 years The severity and position of the wounds are of prognostic importance wounds of the head and neck being especially dangerous There are instances when wounds such as pin pricks after apparently healing are followed by rapidly fatal tetanus A case of one of the authors a girl of 18 years pricked herself with a straight pin in her usual morning toilette and with an incubation period of 5 days died after two days of the disease Ability to take nourishment and severity of spasms often are an index of prognosis Lower and upper limb wounds which are about 6 and 3 times as

frequent a cause of tetanus respectively as trunk and head wounds carry about 10 to 15 per cent less mortality respectively

Early sane debridement betters the prognosis In the Committee for the Study of Tetanus Report for World War I of 30 excised wounds virulent tetanus bacilli were demonstrated but once while in 70 non excised wounds they were found 18 times In order for antitoxin to be of value prophylactically its early use together with prompt and intelligent cleansing of all dirty wounds and removal of foreign bodies and all crushed or devitalized tissues which are apt to serve as a nidus for infection are necessary Caustics and strong antiseptics should be avoided as they will increase the necrosis of tissues thus favoring the growth of microorganisms

Treatment

Control of Spasms

The control of tetanic spasms and convulsions are necessary to ward off asphyxiation to relieve the accompanying pain and to conserve the patient s strength As an emergency measure a volatile anesthetic such as ether may be used For prolonged control of spasms several sedative drugs are useful They may be administered rectally subcutaneously intravenously or intrathecally Rectal administration should be preceded by cleansing enema The latter may necessitate the temporary control of spasms by ether anesthesia or by one of the sedative drugs given parenterally An occasional annoying variable of rectal administration is unusually slow absorption which may greatly nullify the anticonvulsant effect of the administered sedative drug Rarely acute inflammatory involvement of the rectum and still more rarely extensive obstructive lesions will prevent rectal administration

The most efficacious drugs other than volatile anesthetics for control of spasms and convulsions in tetanus are paraldehyde avertin with amylene hydrate the barbiturates chloral hydrate and magnesium sulphate These drugs when administered in efficacious doses are primarily respiratory depressants and a lethal dose causes respiratory paralysis In order to produce the desired anticonvulsant effect in tetanus frequently it is necessary to approach the lethal dose of the drug administered Unfortunately the lethal dose of these drugs varies greatly for the normal person and still more for the patient harboring hepatic renal or cardiovascular disease These drugs should be administered in the smallest dose consistent with the control of spasms or convulsions

The attending physicians and nurses should be alert for the early symptoms of poisoning from the drug being used Occasionally the earliest symptoms of poisoning are excitement and delirium with hallucinations Important danger signals are deep sleep progressing to coma signs of excessive respiratory depression such as markedly slowed respiratory rate with deep inspirations increase of minute volume Cheyne Stokes rhythm and later rapid respiratory rate with shallow inspirations Late manifestations especially with chloral hydrate are those of circulatory collapse i e fall in blood pressure lowered body temperature cyanosis If toxic symptoms appear attention is to be given first to the respiratory condition The nasal passages are to be kept clear oxygen administered and artificial respiration instituted as necessary Strychnine in 2 to 10 mgm doses is administered intramuscularly every two hours The first dose may be given intravenously if the patient is in extremis For circulatory collapse ephedrine sulphate is given intramuscularly in 10 to 30 mgm doses and repeated every hour or two as indicated Intravenous glucose solution aids in raising and maintaining the blood pressure External heat combats fall in body temperature

Paraldehyde possesses a wide margin of safety very large doses rarely causing more than prolonged unconsciousness and thus acute toxicity seldom occurs For these reasons paraldehyde is the drug of choice in those cases in which its anticonvulsant properties are sufficient to control spasms The drug mixed with an equal volume of olive oil or cottonseed oil and 1 c c of benzyl alcohol per 10 c c of paraldehyde is administered rectally Administration is to be repeated as often as necessary to control spasms Acute poisoning after relatively small doses has been reported and toxic symptoms should be watched for It is dangerous to give paraldehyde intravenously

Chloral hydrate frequently is recommended for the control of tetanic spasms It is not a powerful depressant of reflexes and is an inefficient anticonvulsant Furthermore necessary doses of this sedative are dangerously near the lethal dose For the control of spasms chloral hydrate is dissolved in a bland oil such as olive oil or cottonseed oil and administered rectally usually in 1 2 gm dose Ten grams is considered the toxic dose Nevertheless 4 grams have caused death while 30 grams have not proven fatal in reported cases

Of the *barbiturates* sodium phenobarbital 0 3 to 0 7 gm pentobarbital sodium 0 3 to 0 5 gm and sodium amytal 0 4 to 0 8 gm are used commonly as anticonvulsants Depending on the frequency and severity of spasms these drugs are to be given subcutaneously or intravenously Their administration is repeated in amounts and at intervals determined

by the condition of the patient and the degree of control of spasms obtained Only enough of any one of these drugs should be administered to control tetanic spasms because if this amount is exceeded appreciably cessation of spasms may be followed by deep coma and later by respiratory failure Intravenous administration should be made very slowly observing the character of the respirations and the degree of muscular relaxation

Avertin with amylene hydrate is to be given rectally and usually is effective in controlling tetanic spasms It is however to be used with strict adherence to the proper technique in its preparation for administration It is best given by one with experience in its use The dosage varies from 50 to 80 mgm per kilogram of body weight The size of the dose depends on the frequency and severity of the spasms while the frequency of administration is governed by the response to therapy

Magnesium sulfate is an efficacious anticonvulsant It is best given intramuscularly it is much less useful subcutaneously The dose is 0 c c of 25 per cent solution per kilo of body weight In an emergency it may be administered intravenously in 6 per cent solution at the rate of or 3 c c per minute The amount given is that which is necessary to control spasms or to cause the respirations to become slow or shallow Signs of respiratory depression necessitate the intravenous use of 2 5 per cent calcium chloride or better 10 per cent solution of calcium gluconate both administered very slowly

The intrathecal use of magnesium sulfate is highly efficacious in controlling muscular spasms but it is also a more dangerous method than any of those previously described For this method lumbar puncture is performed after the spinal fluid pressure has been reduced to about 100 mm 5 per cent magnesium sulphate solution in amounts of 0 1 c c for each kilo of body weight are introduced If symptoms of respiratory paralysis develop draw off as much spinal fluid as possible and replace with normal saline or Ringer s solution

Curare was first used in the treatment of tetanus by Hoche Since that time until comparatively recently it has been used infrequently because of lack of a standardized preparation Recently Cullen and Quinn used a biologically standardized preparation intracostin with what is described as spectacular relief of symptoms The experience of Adriani and Ochsner with the same preparation was not as promising They did not obtain relief of spasm until almost complete curarization was reached and then the response lasted only twenty to thirty minutes It was necessary to repeat the dose and then respiratory depression and obstruction were avoided with difficulty one death apparently of the five individuals treated being due to curare

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The disadvantage of sedatives is that if amounts adequate to control convulsions are given nutrition and vegetative functions of the patient may be interfered with Furthermore sedatives which depress respiration namely barbiturates and tribromoethanol, have been shown by Firor, Lamont and Schumacker to shorten the life of experimental animals with tetanus Treatment with curare which acts primarily at the motor end plate avoids these disadvantages

It is doubtful that any *antibiotic* will prove useful by virtue of its antibiotic effect on the tetanus bacillus The antibiotics however to combat agents responsible for complications are of distinct value Penicillin has been most useful in infections such as pneumonias developing as a complication In general since complications are comparatively frequent routine use of such drugs as penicillin is advised wherever such complications or dangers of such complications exist

Debridement

This should be done if possible at the time of injury All dead tissue should be removed so as to avoid an appropriate medium for the growth of the tetanus organism If the disease has already set in or it is several days after injury antitoxin should be given at least an hour before debridement Dirty superficial abrasions which are scabbed should have their scabs removed carefully should be irrigated with hydrogen peroxide every four hours and dressed with light porous dressings Deep dirty wounds should

be excised and penetrating wounds opened thoroughly and treated in a like manner All foreign body material should be removed Infected wounds should be cleaned up as much as possible and antibiotics given as indicated by the type and severity of the infection Drainage should be as complete as possible Superficial healing should be prevented If there is a crushing injury of the limb often it is better to amputate The debridement if well carried out probably removes the tetanus organisms from 98 per cent of contaminated wounds

Debridement when the disease has set in is rarely of any value in modifying the course of the disease Much harm will be done if it is done during the height of muscle spasm Increase of spasm and dissipation of toxin might be sufficient added tax on the patient to cause death Debridement frequently is done when the patient s condition has improved or even several months after recovery from the disease

Specific Treatment

Treatment is based upon prevention of damage to the nervous system Antitoxin is given in order to neutralize toxin which has not already reached and become fixed to motor end organs and motor cells in the spinal cord and medulla Trying to accomplish this has resulted in innumerable routines of treatment It is probable that usually not more than 80 000 units are necessary Giving patients a million and a half or more units is not in accord with sane medicine

Infiltration of antitoxin around the wound by multiple injections or proximally around the limb seems logical since it is from this site that the toxin is being disseminated *It is probable that 10 000* units given in this way is adequate in the majority of cases If debridement of the wound is at all adequate the nidus of toxin elaboration should have been largely removed If the wound has not been debrided previously one hour should be waited after giving the antitoxin before the operation is begun so as to have antitoxin present to neutralize any toxin which might escape

An intravenous dose of 50 000 to 150 000 units frequently is given The titre in the blood stream with either dose would seem adequate for a period of two weeks Some prefer to give 5 000 units subcutaneously or intramuscularly daily following the local and intravenous administration and keep the titre up in this fashion

Cole feels that symptoms will appear first before a lethal dose has been absorbed so that if further absorption from wound and through circulation

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involvement is more efficacious Up to a certain time in the incubation it seems that tetanus toxin in the nervou system is neutralizable but as the time increases larger doses of antitoxin are necessary and results become more problematical

In prophylaxis and treatment one must proceed with the feeling that toxin is or is going to be present which antitoxin may succeed in neutralizing thus preventing further harm

Recently Ramon reviewing the work of himself and colleagues suggested giving 75 000 units (U S P) of antitoxin intravenously and 2 c c of tetanus toxoid subcutaneously immediately for treatment of acute tetanus and then at intervals of five to six days 2 and 4 or 6 c c of toxoid We advise use of toxoid in treatment since (1) toxoid can stimulate the antibody producing mechanism of the host better than toxin absorbed from the focus ( ) toxoid can stimulate evenly and in known amounts (3) the patient may have had a subclinical exposure or exposures to tetanus toxoid or toxin and the dose of toxoid may be absorbed rapidly enough and in sufficient quantity to be beneficial in stimulating the immunity mechanism (4) toxoid reaching the nervous system may react with antitoxin and enhance neutralization of toxin because of more rapid accomplishment of optimal proportions for the reaction (5) the work of Jones and Jamieson on guinea pigs which may have a bearing in the human being showed that tetanus spores and calcium chloride ideal for production of tetanus cause no increase in antitoxin titre in immunized animals i e animals previously exposed to antigenic stimulus while another dose of toxoid causes marked increase (6) toxoid can do no harm

Toxoid and antiserum for prophylaxis and treatment are advisable in the unimmunized and toxoid in the immunized Undoubtedly most of the population has been exposed through soilage of wounds and ingestion to the tetanus organism with in some cases one or more instances of absorption of toxin and resultant antigenic stimulus The case of tetanus needs every possible chance for recovery In some cases of tetanus toxoid may stimulate an otherwise too latent but previously somewhat conditioned antibody producing mechanism in the host This possibility makes use of toxoid as a booster imperative in treatment Evidence that some individuals possess antitoxin in their blood stream without having received antitoxin or having had tetanus further establishes the feasibility of administration of toxoid in the hope that it may stimulate to effective action the antitoxin and other protective mechanisms of the host

can be stopped recovery is a matter of time He advises 200 000 units intravenously in one dose This dose gives 10 units per c c at the end of 7 days and 3 65 at the end of 14 days which ordinarily is considered adequate He uses avertin given as in a basal anesthesia for control of spasm In very severe cases he gives 2 to 3 such doses daily for as long as 7 days In milder cases large doses of bromides chloral nembutal and rectal paraldehyde are recommended

Yener claims on excluding cases which die in the first 24 hrs a mortality of 19 3 per cent He induces a light narcosis with chloral hydrate 0 6 to gm (gr 10 to 30) 1 hour before treatment of any kind He then encircles the wound with 0 000 units of antitoxin An hour later the lesion is excised widely and thoroughly and if of a limb after the limb has been encircled with 40 000 units proximally Twenty thousand units then are given intracisternally slowly by gravity About 8 hours later 40 000 units diluted with 300 to 400 c c of normal saline are given intravenously and 3 hours after this 1 gm (gr 15) methenamine is given in 10 per cent solution intravenously An hour later a second intravenous dose of 40 000 units is given Another 40 000 units may be given around the limb or wound or intravenously 6 hours later and methenamine may be repeated 10 to 1 hours after each intramuscular injection

There are many variations of treatment Some give much of the medication intrathecally while others divide it over the various sites Intracisternal and intraspinal medication frequently are accompanied by serious reactions These methods of administration have no advantage and are inadvisable Since there are more reactions with intravenous administration than intramuscular where no advantage is gained by intravenous administration the intramuscular route should be selected

In this country tetanus antitoxin is defined in terms of American units One unit is ten times the amount of antitoxin which when mixed with one standard test dose of toxin 100 minimal lethal doses and allowed to stand 1 hour will prevent the death for four days of a 350 gm guinea pig injected subcutaneously The international unit of tetanus antitoxin is one half the American unit

If administration of antitoxin is delayed more should be given in prophylaxis and treatment Firor and coworkers have shown that it takes enormously larger doses of antitoxin to prevent symptoms in dogs if the toxin is placed in the brain and the cord than if placed elsewhere In the patient therefore the area reached by the toxin and the possible amount of toxin must be considered Likewise antitoxin injected directly into the area of

a suitable antibiotic is to be given Experience with penicillin proves it to be of great value

Because of the ease with which the hypersensitive reflexes are stimulated causing muscular spasms measures to prevent stimulation are of essential importance Also as soon as possible the patient should be placed in a darkened room kept at a temperature of 68 to 70 F The most exacting quietude and freedom from all possible external tactile thermal and other stimuli must be enforced The patient is to be placed under constant nursing supervision preferably by nurses experienced in managing this disease It is emphasized that retention of urine commonly is present requiring catheterization using aseptic technique The bowels are constipated and this necessitates the use of mild cathartics or of enemata

The diet should be nutritious The method of administering food and liquid will depend on the degree of trismus and on the presence or absence of interference with deglutition When necessary saline and glucose solution can be given intravenously, both food and liquids may be introduced through a small tube the latter introduced through the nose or orally after extracting a tooth if that is necessary Because of the excessive sweating the amount of liquid given should seldom be less than 2 000 c c a day Often the patient can ingest such foods as milk thin gruels solutions of food stuffs such as dissolved aminoids suspensions of the commercially prepared baby foods containing most of the essential food elements thin custards egg yolk beaten up in orange juice and fruit juices These substances can be given also through the small stomach or nasal tube It may be emphasized that the amount of muscular energy a tetanus patient expends makes it seem rational to feed an ample supply of carbohydrate If the diet used must be of such character that it is deficient in the vitamin B group this complex can be added readily in concentrated liquid form

Special symptomatology will indicate the use of special remedial measures For example when the spasmodic muscular seizures are unusually severe intraspinal pressure may be increased Under such circumstances Chapman and Miller have found that this may be relieved by lowering the pressure by means of spinal puncture Partial asphyxiation due to laryngeal spasm may be relieved by administering oxygen however tracheotomy occasionally will be necessary Respiratory paralysis is combated by artificial respiration preferably using the respirator Before discharge the dorsal spine should be x rayed As many as 20 / of some series have shown compression fracture Such fractures respond readily to orthopedic measures

Management of the Usual Type of Tetanus

Much that is controversial and contradictory has been written concerning the therapeutic management of tetanus One reason for this situation is that almost without exception no one physician has had sufficiently large clinical experience with the disease to give an authoritative conception of its treatment Another reason is that the disease varies greatly in the extent of its clinical manifestations and in its mortality For this reason the following brief discussion of the management of tetanus can only represent the tentative conclusions based on the authors observations combined with those that have been reported Furthermore, it is emphasized that each case of tetanus is to be treated individually i e modifying the management to suit each particular patient and his surroundings

The treatment of the individual patient with tetanus consists usually first in controlling the spasmodic contractures This is accomplished by the use of sedative and/or muscle relaxing drugs, which have been described It is our custom to use first paraldehyde or one of the barbiturates If these fail of their purpose, avertin then is used However, the physician will do well to use the sedative drugs with which he has had the most clinical experience Preparations of curare in wax or oil should be used to relieve severe muscle spasm and reduce the amount of sedative needed where there are no contraindications and where the physician can watch the patient continuously For the reasons previously discussed proper sedation and relief of muscle spasm is to be maintained throughout the course of the disease

Just as soon as the reflex muscle irritability will permit the patient is tested for allergy to the antitoxin and desensitized if necessary by the procedures already described If the patient s condition is favorable and a debridement is indicated the region surrounding the wound is infiltrated with from 10 000 to 20 000 units of antitoxin However if the wound is on a limb, the infiltration usually will best be done by encircling the latter proximal to the wound A period of one hour is allowed to elapse after this infiltration with antitoxin, and then the wound is debrided surgically Following this procedure the patient is given 60 000 units of antitoxin intravenously and/or intramuscularly and coincidentally the first immunizing dose of 1 c c toxoid is administered This amount of antitoxin usually will suffice If the wound becomes septic or if the symptoms have not improved greatly at the end of about five days then an additional 20 000 units should be given

If the disease is complicated by sepsis or there is danger of complications

a suitable antibiotic is to be given Experience with penicillin proves it to be of great value

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Gas Gangrene

A discussion of tetanus is not complete without some consideration of gas gangrene because (1) similar conditions are necessary for the establishment of the disease, (2) both diseases occur with like conditions of injury, (3) certain principles of their treatment are the same, (4) the antitoxins for both conditions frequently are mixed, (5) both are caused by anaerobes.

Gas gangrene is defined as a localized but often rapidly spreading or metastasizing acute necrotizing infection of a wound especially, though not exclusively, involving muscle with massive edema, gaseous infiltration, discoloration with often but not always putrefactive odor. Crepitation and ability to push the gas about in the tissues on pressure together with discoloration are responsible for the name. In severe cases there is general toxemia, anemia, apathy, delirium, shock with collapse and at times septicemia.

Onset of the condition after infliction of injury may be as early as 4 to 5 hours beginning with exudation of frothy brownish fluid, emphysema and edema, even noticeably spreading on examination, with collapse and death within the day. On the other hand the condition may not become known for several days with the so-called strictly localized gas abscess showing swelling and crepitation but no systemic effect.

Pease, studying 308 cases in World War I, found causative anaerobic organisms in the following proportions: *Cl. welchii* 85 per cent, *Cl. septicum* 17.5 per cent, *Cl. novyi* 1.6 per cent. Since all of these organisms have tissue toxins and are saccharolytic, i.e., use sugar with resultant gas production, they are capable of producing gas gangrene. Other organisms such as *Cl. sporogenes*, which digest proteins but are not toxic in themselves, are present frequently, 35.4 per cent, often accounting for the putrefactive odor and possibly through their action furnishing food for the saccharolytic organisms.

The above organisms are not always present where gas is developed. There are instances in debilitated individuals in which the aerobic colon bacillus gaining entry to a large area of subcutaneous fat produces gas by digestion of sugar in the tissues. The streptococcus hemolyticus and staphylococcus albus together and many other organisms and organismal combinations, both aerobic and anaerobic, may produce gas infection. In these instances, however, it is doubtful whether the classical picture of severe gas gangrene ever is present. Findings of many investigators that gas forming anaerobes, potential toxin producers, may be present in the

liver and other tissues apparently before and after death is confusing and as yet unexplained

Recently a new type of gas gangrene has made its appearance in war industrie Contamination of wounds with magnesium particles produces a gas gangrene with evolution of hydrogen

In World War II the percentage of organisms producing gas gangrene appears similar to World War I Cases in war are of a younger group than under peace conditions A mortality of 53 pe cent has been recorded by Franz while for the civilian population it has been estimated by Kummel to be as high as 85 per cen

In 44 cases of the civilian population studied by us 7/ per cent were over 40 years of age and there was a mortality of 43 per cent However the majority of our cases were debilitated affected with vascular disease diabetes obesity syphilis necrotizing injuries This mortality therefore suggests that gas gangrene often was a terminal event and only in part the cause of death

In World War II Jeffrey s statistics suggest an incidence among wounded of 0 25 per cent of the severe type while the localized type is not uncommon In the latter simple incision and drainage is all that is necessary The figure 0 5 per cent compares with that of 0 3 per cent for 1 300 German troops in World War I

In comparing gas gangrene with tetanus we find both conditions caused by anaerobes both conditions requiring accessory conditions such as injury aerobes splinters etc both having spores capable of lying dormant in a scar probably gas gangrene anaerobes to a lesser extent but gas gangrene flourishing especially where there is an additional factor debilitation usually in the form of a disease with lesions in blood vessels serving to reduce or shut off nutrition The tetanus toxin is a neurotoxin and the gas gangrene toxin a histotoxin

Diagnosis is made culturally as with Cl tetani and by injecting a rabbit or guinea pig intravenously with the material killing the animal with a blow over the head after 5 minutes and incubating overnight If gas gangrene organisms are present the animal will be tremendously bloated and the liver filled with holes due to gas Both wound material and blood of the patient are to be used for diagostic tests Typical organisms also may be seen in smears made from infected tissue

The gas gangrene organisms are more prevalent in the soil sometimes in as many as 100 per cent of samples and in the intestinal tract of man than the tetanus organism yet in our survey of cases they were only two thirds a numerous as tetanus cases

Spores without toxin are innocuous are taken up by monocytes and apparently reach various organs such as the liver where they may germinate and be destroyed unless there is sufficient histotoxin or other conditions furthering proliferation and toxin production in which case a generalized disease develops

Gas gangrene occurs in battle especially after compound fractures gunshot and other wounds contaminated with missiles wads mud gravel bits of clothing detached skin fragments where there is fecal contamination as in gangrenous appendix criminal abortion wounds of the perineum and on hypodermic injections of an irritating medicant In the early part of World War I as many as 10 to 1 per cent of those wounded developed gas gangrene With adequate asepsis and debridement the figure was reduced to 1 per cent Reports for civilian populations give accident series showing as low as 0 16 per cent

Gas gangrene may recur suggesting lack of permanent immunity in at least some cases Toxoids can be produced and apparently can be used to protect they are used in antitoxin production in horses, their role has not been investigated sufficiently It is unlikely that they will reach for some time even if efficacious the widespread use of tetanus toxoid in human beings

In wound prophylaxis the following mixture is used frequently *Cl tetani* antitoxin 1 500 units *Cl welchii* antitoxin 2 000 units *Cl septicum* antitoxin 000 units

In treatment the following combination is used *Cl welchii* antitoxin 10 000 units *Cl septicum* antitoxin 10 000 units *Cl histolyticum* antitoxin 2 500 units *Cl oedematiens* antitoxin 1 000 units *Cl aedematoides* antitoxin 00 units contained in one vial One to four vials of this mixture should be administered intravenously immediately and repeated in 4 or 5 hours and continued daily as indicated Intramuscular injections around the wound and oxygenation of the wound are suggested by some Apparently the mortality is reduced by serum but in civilian populations where older groups of patients are concerned the value of serum does not seem particularly evident Sulfonamides in the wound are valuable apparently sulfadiazine is best followed by sulfathiazole and sulfanilamide in order of efficiency

Penicillin in general has proven more efficacious in gas gangrene than the sulfonamide compounds Fisher et al after a study of 436 cases concluded that penicillin should be used rather in prevention than treatment It is advisable to administer penicillin at the time of and 3 5 days after primary debridement as recommended by Jeffrey and Thompson It is

felt that this will do much to arrest the progressive myositis Altheimer, Furste and Culbertson suggest penicillin parenterally as soon as possible and in conjunction with surgical treatment in persons with gas gangrene or with wounds of the type which predisposes to its development and to continue using it thereafter both preoperatively and postoperatively in large doses up to 1 000 000 units every three hours until the threat of this infection is over

Zinc peroxide in the wound has proven valuable except possibly where *Cl welchii* is the etiological agent Amputation and debridement where necessary must be done immediately Plaster immobilization of extremities apparently has been beneficial in some cases Good surgical judgment is necessary

X ray may be valuable in diagnosis of the condition Bubbles and streaks of gas are looked for Some have advised x raying all injuries to look for gas and have advocated portable machines in the army field hospitals for this purpose and for treatment of the condition Certain workers feel x ray is invaluable in treatment others are not convinced The principles underlying its value are said to be generation of hydrogen peroxide in the tissues as a result of the radiation

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CHAPTER X

ANTHRAX

By CALDERON HOWE

Table of Contents

Synonyms — Anthrax charbon malignant carbuncle malignant edema woolsorters or ragsorters disease (English) charbon bacteridienne oedeme malin fievre charbonneuse fievre bacteridienne (French) antrace febbre carbonchiosa (Italian) Anthrax Milzbrand Milzbrandfieber Hadernkrankheit Karbunkelkrankheit (German) antrax carbunclo (Spanish)

Definition — Anthrax is a specific infectious disease of animals chiefly herbivora frequently transmitted to man from infected animals or their products Almost always fatal in animals it is characterized by varying mortality in man depending on the type and extent of infection The causative agent is the *Bacillus anthracis*

History

The name of the disease is derived from the Latin *anthrax* and the Greek ἄνθραξ meaning a live coal or carbuncle Many descriptions

conforming to the common types of anthrax are found in the ancient literature. In the 17th and 18th centuries there were numerous accounts of "anthrax" in man and animals which, although accurate as far as they went, probably included many other pustular and septicemic conditions which could not be readily differentiated. It was not until 1850 that the anthrax bacillus was first noticed, albeit in a very cursory manner, by Rayer in the examination of the blood of sheep dead of the disease[3]. Pollender in 1855[3, 4] described the organisms more fully as he found them in the blood and spleen of anthrax cows, and Brauell in 1857 was the first to note the presence of the same type of rod in human anthrax blood. The latter worker also showed that the disease was transmissible to a wide variety of animals. Davaine, in a series of detailed experiments, showed as conclusively as could be expected without means of cultivation that anthrax was caused by a living organism that multiplied in the body, invaded the bloodstream and produced death by septicemia. This organism Davaine termed "bactéridie," a name by which it is still known among French writers. Subsequently Davaine and Raimbert[8] found the same organism in a "malignant pustule" in man, thus demonstrating the etiological identity of the disease in man and animals. The final proof of the causative role of *B anthracis* was produced by Koch[9], who gave a full account of the organism, described for the first time its formation of resistant spores, its cultivation in vitro, the reproduction of the disease by the injection of pure cultures and the recovery of the organism from the animals at necropsy. These now famous "postulates" have been linked with his name ever since. Successful immunization of animals was carried out first by Pasteur in 1881 in a series of classical experiments[10] using what he took to be attenuated cultures of *B anthracis*. His observations were the starting point for methods developed later and universally adopted for controlling outbreaks of animal anthrax. In 1894 Eppinger[11] in a treatise which remains unexcelled both in accuracy and completeness of observation was among the first to establish pulmonary anthrax in man as a clinical and pathological entity, relating it as well to other forms of anthrax infection.

Etiology

Bacillus Anthracis

Morphology[1, 13, 14].—*B anthracis* occurs in the blood and organs of infected animals and humans as a straight sharply square ended rod

measuring 5 to 10 micra in length and 1 to 1 5 micra in width usually single sometimes united to form short chains of two or more bacilli In cultures these chains grow to long sinuous filaments suggesting bamboo in appearance in which the bacilli are somewhat shorter usually 3 to 4 micra in length The young unstained bacillus is homogeneous and practically without internal structure but older involutional forms may be finely granular *B anthracis* is nonmotile and is well stained by any of the basic aniline dyes It is gram positive and a capsule can be demonstrated readily by the usual methods being visible in routine stain preparations as a clear area of uniform width around each cell The size and prominence of the capsule may vary with different strains Its formation is promoted by increasing the carbon dioxide tension of the medium The formation of spores occurs in the dead animal body and in culture media in the presence of free oxygen Spore bearing forms are never found in the living animal tissues or blood The spores are ellipsoidal or oval in shape are found equatorially in the bacillus and germinate by polar rupture

Cultivation and Resistance — B anthracis is grown easily under aerobic conditions on all ordinary nutrient media giving within 24 hours a characteristic appearance On nutrient agar the colonies have a ground glass opalescence and at the margins there are feathery outgrowths which under the microscope are seen to be composed of long curled unbranching chains of bacilli There is slight hemolysis on blood agar In gelatin stab cultures the border filaments are more conspicuous growing into the medium at right angles to the line of the stab giving the appearance of an inverted fir tree In broth a flocculent turbidity develops individual flocculi falling to the bottom of the tube Capsulation is favored by increasing the carbon dioxide tension to 10 to 15 per cent[15] As will be pointed out later there appears to be a definite correlation between capsule formation and virulence but none between spore formation and virulence Spores appear more slowly in cultures of *B anthracis* than in other members of the *Bacillus* group Both virulent and avirulent strains may be either sporogenous or asporogenous Under certain conditions of cultivation such as incubation below 16 C or above 4[illegible] C the power of sporulation may be lost permanently Incubation at 4[illegible] C also causes a gradual increase in the incidence of avirulent variants in a given culture[9] Furthermore true smooth and rough variants which do not form spores or capsules have been isolated by micromanipulating techniques[1]

Nutritional studies have shown that an interrelationship exists be

tween certain amino acids of similar chemical composition in their effect on the growth of *B. anthracis*[18]. Recent work has demonstrated that thiamine is the only vitamin required for the growth of this organism and that various metallic ions have a striking stimulatory effect on growth, for which it is thought they too might be required[19]. As a result practical protein-free media of exactly known chemical composition have been devised for large scale cultivation and maintenance of virulence.[6]

Asporogenous anthrax bacilli show very little resistance to heat and drying and cultures will not survive in a medium more than a few weeks. There has been good evidence that spores will germinate after being stored in the dry state for as long as 40 years.[1] A temperature of 135° C. for 5 to 10 minutes is necessary to kill dry anthrax spores in the absence of surrounding moisture, but spores suspended in normal saline are killed at 100° C. in 5 to 10 minutes. Spores are also killed by 5 per cent cresol in 7 hours, by 5 per cent phenol in 2 days and by 10 per cent mercuric chloride in 20 minutes.

Pathogenetic and Immunochemical Relationships

Many theories as to the mode of action of *B. anthracis* in the animal body have been proposed but have remained unsubstantiated by experimental proof. For instance, the effects of anthracemia have been ascribed to the possible reduction of oxygen tension to critical levels of unsaturation by large numbers of actively dividing bacterial cells. Convincing evidence for this explanation is lacking as it is for the postulation that the essential disease process is one of mechanical blockage of smaller blood vessels and capillaries by masses of circulating organisms. The existence of a true anthrax exotoxin likewise has remained unproven although occasional early investigators were able to reproduce the histopathological changes characteristic of anthrax lesions by crude extracts of the organism.[3] It is of historical interest that such observations correspond in many ways with more recent biochemical and biological researches which have thrown considerable light on the pathogenetic and immune mechanisms in susceptible and resistant animal species.

Crude extracts of anthrax skin lesions produced in rabbits have been fractionated and the fractions partially purified, resulting in the isolation of an inflammatory (IF)[21] and a protective antigen (PA). When injected into susceptible animals, the inflammatory factor was found to

cause tissue changes identical with those produced by actual anthrax infection except for the presence of organisms These changes consisted of spreading edema fragmentation of the collagenous connective tissue areas of hemorrhage and infiltration of damaged tissue by leucocytes and mononuclear cells This tissue reaction since it is not the result of actual infection might well be called an anthracoid lesion The inflammatory factor was found to have the ability also to interfere with the normal blood clotting mechanism Chemical electrophoretic and spectrophotometric analyses showed it to be closely related to but not identical with glutamyl polypeptide known to be the chief component of the capsule of *B anthracis*[18] Glutamyl polypeptide happens also to be common to a number of other species of gram positive spore forming organisms such as *B subtilis*[18] and *B mesentericus*[1] Failure to produce any tissue reaction with pure glutamyl polypeptide obtained from *B anthracis* grown in culture in contrast to the anthracoid lesion produced by the inflammatory factor suggests that the capsule produced in vivo has biological properties different from the capsule produced in vitro in addition to or because of chemical conditions peculiar to the tissue reaction Whatever its composition in vivo the importance of the capsule of *B anthracis* in the pathogenesis of anthrax lesions will emerge from the ensuing discussion

In exploring the problem from the point of view of the host it has been found in studying the course of experimental animal infection that the natural resistance of a given species is commensurate with the degree *to which leucocytes accumulate at the site of intracutaneous inoculation* with anthrax spores[19] Thus in the immune type of response occurring in naturally resistant species or in susceptible species immunized with protective antigen (PA) (see Fig 1) leucocytes are plentiful and the organisms developing from recently germinated spores rapidly losing their capsules and staining qualities promptly disappear from the lesion In the non immune type of response occurring in susceptible species leucocytes are scarce and encapsulated organisms continue to proliferate until the death of the animal supervenes This close association of leucocytes with the loss of capsule and disintegration of the organisms led to the isolation from animal leucocytes and other tissues of an anthracidal substance (AS)[20] Similar anthracidal substances had been known many years previously to be present in leucocytes[21] and they have been found to be present to a significant degree in normal rabbit serum The anthracidal substance from leucocytes is neutralized in vitro by the inflammatory factor described above but not by capsular glutamyl polypeptide

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animals against infection from spore inoculation.[9] There has been some evidence of late that at least one type of protective antigen from such sources represents a combination of polysaccharide and protein.[40] The second fraction (PA) isolated from the crude extracts mentioned earlier was found on electrophoresis to migrate between the gamma and the beta globulins. This protective antigen caused a high degree of immunity in species ordinarily susceptible both to intracutaneous inoculation and to inoculation by the respiratory tract of virulent anthrax spores.[41] One further and significant step toward the elucidation of this complex problem has been the isolation of a protective antigen from filtrates of *B. anthracis* cultured in plasma or serum of various animals.[4, 4] It is fully as potent as the protective antigens previously isolated from anthrax edema fluid and differs from the latter in not being associated with any inflammatory factor. Its production in vitro obviates the necessity for any tissue reaction in its formation in contrast to the inflammatory factor which results only from the proliferation of anthrax organisms within the animal body. Neither does it seem to be present preformed in the organism, thus suggesting that it is distinct from the antigens of the cell and is an extracellular product of bacterial metabolism in this particular environment rather than a product of autolysis.

All of the above deductions apply to animal anthrax, but many similarities between animal and human anthrax, both pathological and clinical, support the belief that the same principles may be operative in all species. The fact that approximately 90 per cent of human anthrax cases are either localized lesions, so called malignant carbuncles, or malignant edema, indicates that man is naturally relatively resistant to invasion by *B. anthracis*. Thus in a series of 25 cases seen by the author[43] which resulted from infection with strains of anthrax known to be highly virulent for animals, the lesions invariably were well localized, there was transient bacteremia in three instances, and no fatalities occurred. The difficulties in evaluating chemotherapy in the presence of such apparently great natural resistance will be discussed in a later section.

It is possible that recovery from anthrax in man may confer increased resistance to subsequent reinfection, since rare instances have been reported in which a second malignant pustule has been much milder than the initial lesion preceding it by many months.[44, 4] Such reports, however, do not take into consideration the variation in pathogenicity among strains of anthrax bacilli from different sources. Furthermore, several cases have been reported recently to the author in which proven anthrax

has been observed on two or three different occasions in the same individual[16]

Pathology

The essential pathological change in human anthrax is identical with that seen in animals, namely, edema, varying degrees of cellular infiltration, liquefaction necrosis and hemorrhage. In the majority of cutaneous lesions, which are relatively localized and usually non fatal, there is extensive leucocytic infiltration. There seems to be some correlation in man, as there is in experimental animal anthrax, between the degree to which leucocytes accumulate at the site of infection, if it is localized, and the apparent resistance of the individual host. The absence of true pain in such lesions appears to be referable to axonal degeneration of the non medullated and medullated nerve fibers in the skin[1]. In contrast, in rapidly fatal cases, where there is generalized infection, post mortem changes will be widespread, consisting of gelatinous, serous and hemorrhagic effusion into the various tissues with localized areas of necrosis and ulceration. Thus in malignant edema, leucocytic infiltration is minimal and edema is the cardinal feature in the skin[101].

In pulmonary anthrax the lungs may be consolidated or edematous to varying degree and the bronchi and bronchioles contain the characteristic bloody exudate. Pleural effusions as well as pleuritis are common findings. The outstanding histological changes usually are marked hemorrhagic congestion and almost total absence of polymorphonuclear cells even in the areas of liquefaction necrosis. Occasionally large numbers of mononuclear cells laden with hemosiderin are seen[104]. There is hemorrhage into all the hilar lymph nodes, which appear black and congested. Thrombosis of small vessels is encountered often and anthrax bacilli are seen in most of the tissues. Lesions resembling the malignant carbuncle have been described as occurring in the trachea and larger bronchi[73] but such foci are the exception rather than the rule.

In intestinal anthrax there may be hemorrhagic or serofibrinous peritonitis with necrotic mucosal ulcers. All organs are seen to be hyperemic and the entire gastrointestinal tract may be filled with bloody fluid. Anthrax bacilli are easily isolated from any of the tissues. In some instances they have been seen to accumulate in the mesenteric lymph nodes and the Peyer's patches of the bowel, as do typhoid bacilli in typhoid fever[10].

animals against infection from spore inoculation.[9] There has been some evidence of late that at least one type of protective antigen from such sources represents a combination of polysaccharide and protein.[10] The second fraction (PA) isolated from the crude extracts mentioned earlier was found on electrophoresis to migrate between the gamma and the beta globulins. This protective antigen caused a high degree of immunity in species ordinarily susceptible both to intracutaneous inoculation and to inoculation by the respiratory tract of virulent anthrax spores.[11] One further and significant step toward the elucidation of this complex problem has been the isolation of a protective antigen from filtrates of *B. anthracis* cultured in plasma or serum of various animals.[4, 42] It is fully as potent as the protective antigens previously isolated from anthrax edema fluid and differs from the latter in not being associated with any inflammatory factor. Its production in vitro obviates the necessity for any tissue reaction in its formation in contrast to the inflammatory factor which results only from the proliferation of anthrax organisms within the animal body. Neither does it seem to be present preformed in the organism, thus suggesting that it is distinct from the antigens of the cell and is an extracellular product of bacterial metabolism in this particular environment rather than a product of autolysis.

All of the above deductions apply to animal anthrax, but many similarities between animal and human anthrax, both pathological and clinical, support the belief that the same principles may be operative in all species. The fact that approximately 90 per cent of human anthrax cases are either localized lesions, so-called malignant carbuncles, or malignant edema indicates that man is naturally relatively resistant to invasion by *B. anthracis*. Thus in a series of [illegible]5 cases seen by the author[43] which resulted from infection with strains of anthrax known to be highly virulent for animals, the lesions invariably were well localized, there was transient bacteremia in three instances, and no fatalities occurred. The difficulties in evaluating chemotherapy in the presence of such apparently great natural resistance will be discussed in a later section.

It is possible that recovery from anthrax in man may confer increased resistance to subsequent reinfection, since rare instances have been reported in which a second malignant pustule has been much milder than the initial lesion preceding it by many months.[44, 4] Such reports, however, do not take into consideration the variation in pathogenicity among strains of anthrax bacilli from different sources. Furthermore several cases have been reported recently to the author in which proven anthrax

been isolated from spinose ear ticks occurring naturally on anthrax animals[43] and has been shown to be transmissible experimentally in animals by biting flies[4] The ingestion of infected imported foodstuffs has been held responsible in many instances where cases have occurred in previously uninfected territory [9]

The most susceptible animals are the herbivora chiefly cattle sheep pigs horses and goats Despite occasional mild cases the mortality appears to be very nearly 100 per cent The disease as a rule results from ingestion of spores and takes the form of a septicemia varying from a sudden apoplectic attack with death occurring within a few minutes or a few hours after the onset of symptoms to a subacute variety manifested by fever and frequently by intestinal or pneumonic symptoms terminating fatally in a week or less In horses and mules circumscribed swellings or carbuncles may appear at the sites of infected fly bites and are not unlike the malignant carbuncle of human anthrax

Depending on the rapidity of the invasive process the pathological changes seen in animal anthrax are chiefly those resulting from septicemia Widespread hemorrhages serous effusions edema and engorgement of the liver spleen and kidneys will be observed The abdominal organs are extremely friable and contain the vegetative anthrax bacilli in huge numbers Most characteristic are the black color and the incoagulability of the blood the latter accounting for the extreme hemorrhagic tendency Spores are found in the discharges In the subacute forms where there may be isolated lesions resembling the relatively localized process seen in human anthrax the pathological changes resemble closely those described in association with experimental animal anthrax in the more resistant type of host

Recent studies[41, 61] have shown that anthrax produced by inhalation of anthrax spores is not a true pulmonary disease but is a systemic disease similar to that resulting from infection induced by injection or via the alimentary tract There appears to be little or no reaction of the lung tissue to the spores in experimental animals exposed to spore clouds and the fatal dose by this route is much greater than that by injection of spores under the skin Invasion of the host by inhaled anthrax spores apparently occurs through the lymphatic system the bronchial lymph nodes being the chief site of germination of spores and multiplication of vegetative forms Pathological changes become apparent only after terminal bacillemia is established and these consist of active hyperemia with some hemorrhage and the presence of bacilli in all vessels and to some extent in the alveolar walls

Anthrax of the central nervous system usually is associated with internal anthrax but may be a terminal complication of initially external malignant edema, particularly those cases with primary involvement of the face and neck.[106] The lesions in the brain in anthrax are essentially extravascular and meningoencephalitic. The acute hemorrhagic nonpurulent nature of the inflammation with destruction of tissue by edema is similar to that produced by anthrax in other parts of the body. There may be blood in the leptomeninges as well as multiple hemorrhages into the brain substance. Microscopic examination reveals marked edema of the vessel walls, relatively little leucocytic infiltration and the widespread presence of anthrax bacilli.

Animal Anthrax

Anthrax is known to occur in nearly every country in the world. As a rule it seems to be commoner in swampy, low lying country with warm, loose, moist soils. In such areas, known as "anthrax districts," animals are sporadically infected, chiefly during the summer months but may become infected at any time of the year. In some seasons losses in anthrax districts may be comparatively light and the cases may be more or less spotty in their occurrence. In other years the disease assumes a highly virulent form appearing simultaneously at a number of places, spreading rapidly to new areas and causing heavy losses of livestock in the proportions of a major epizootic. The cause of these fluctuations is unknown but has been thought to be related to climatic variations since major outbreaks often follow hot, dry summers with scant growth of herbage necessitating grazing close to the soil.

The mode of spread of the infection hinges on spore formation by *B. anthracis*. During the terminal stages of anthrax in animals large numbers of bacilli are excreted in the urine and feces. The severe hemorrhagic tendency induced by anthracemia causes exudation of bloody fluids from the other body orifices at the time of death. The bacilli promptly sporulate on having access to free oxygen outside the animal body, and the spores may remain virulent in the soil for years. Animals grazing on contaminated pasture thus are liable to ingest infected soil with the forage, and the cycle is continued. An accessory mode of spread has been found in various types of biting flies which usually are seen in abundance on unburied anthrax animal carcasses[4] and may carry the infection to other animals and thus to other areas. *B. anthracis* has

been isolated from spinose ear ticks occurring naturally on anthrax animals[48] and has been shown to be transmissible experimentally in animals by biting flies[4]. The ingestion of infected imported foodstuffs has been held responsible in many instances where cases have occurred in previously uninfected territory.[9]

The most susceptible animals are the herbivora, chiefly cattle, sheep, pigs, horses and goats. Despite occasional mild cases, the mortality appears to be very nearly 100 per cent. The disease as a rule results from ingestion of spores and takes the form of a septicemia varying from a sudden apoplectic attack with death occurring within a few minutes or a few hours after the onset of symptoms to a subacute variety manifested by fever and frequently by intestinal or pneumonic symptoms terminating fatally in a week or less. In horses and mules circumscribed swellings or carbuncles may appear at the sites of infected fly bites and are not unlike the "malignant carbuncle" of human anthrax.

Depending on the rapidity of the invasive process, the pathological changes seen in animal anthrax are chiefly those resulting from septicemia. Widespread hemorrhages, serous effusions, edema and engorgement of the liver, spleen and kidneys will be observed. The abdominal organs are extremely friable and contain the vegetative anthrax bacilli in huge numbers. Most characteristic are the black color and the incoagulability of the blood, the latter accounting for the extreme hemorrhagic tendency. Spores are found in the discharges. In the subacute forms, where there may be isolated lesions resembling the relatively localized process seen in human anthrax, the pathological changes resemble closely those described in association with experimental animal anthrax in the more resistant type of host.

Recent studies[49, 51] have shown that anthrax produced by inhalation of anthrax spores is not a true pulmonary disease but is a systemic disease similar to that resulting from infection induced by injection or via the alimentary tract. There appears to be little or no reaction of the lung tissue to the spores in experimental animals exposed to spore clouds, and the fatal dose by this route is much greater than that by injection of spores under the skin. Invasion of the host by inhaled anthrax spores apparently occurs through the lymphatic system, the bronchial lymph nodes being the chief site of germination of spores and multiplication of vegetative forms. Pathological changes become apparent only after terminal bacillemia is established and these consist of active hyperemia with some hemorrhage and the presence of bacilli in all vessels and to some extent in the alveolar walls.

The control of animal anthrax depends on the effective disposal of infected carcasses chiefly by deep burial in quicklime, to minimize ground contamination and even more on the efficient and timely use of active immunization of herds in the anthrax season The type of vaccine most widely used consists of living spores attenuated in virulence either in aqueous suspension or combined with saponin [3] The addition of the latter agent is predicated on the experimental observation that non specific irritants causing local inflammation will create a barrier against the development and spread of anthrax lesions resulting from the injection of spores at the same site [4] Care always should be taken against contamination of the ground with spore vaccine and the possibility kept in mind that occasional animals particularly susceptible will develop anthrax septicemia as a result of spore vaccine inoculation It has been found that immunity or increased resistance conferred by any of the specific immunizing agents lasts not much longer than 9 months to a year

Anthrax in Man

Incidence and Mortality

Anthrax in man results solely from contact with diseased animals or with animal products in which the highly resistant anthrax spores persist[5] So called industrial anthrax occurs in persons handling hides [6] and raw wool products Thirty-seven to forty-six per cent of all cases occur in the tanning industry and 8 to 34 per cent of all cases occur in trades handling wool animal hair and bristles Occasional cases still are traced to shaving brushes made with infected animal hair formerly a major source of anthrax [6] Elephant tusks used in the ivory industry have been implicated in rare instances [7] Non-industrial anthrax comprising 11 to 16 per cent of all infections occurs in farmers butchers veterinarians and others coming into close contact with diseased or dead animals Outbreaks of human anthrax have been traced occasionally to handling or eating infected raw meat[60] [1] but no authenticated case of man to man transmission has been reported However, intrauterine infection of the human fetus has been recorded[6]

The incidence of human anthrax in the United States according to state health department reports covering the years 1919 to 1943[63] has amounted to less than a hundred cases annually most of them in the last few years occurring in connection with the tanning or wool industries

In European countries particularly Russia and the Balkans as well as in Asia human anthrax is apparently still of frequent occurrence consequent upon its wide prevalence in animals[61] Stringent measures to insure the disinfection of imported wool as well as widely practiced anthrax immunization of herds has kept anthrax in England under fairly good control[4]

The mortality of anthrax in general as well as can be judged from the fatalities among reported cases has varied from o to 40 per cent That of internal anthrax however approaches 100 per cent although there are rare instances where treatment has been instituted promptly enough in which recovery has taken place[63] The mortality in external anthrax is of course less when uncomplicated being in the neighborhood of 16 to 20 per cent There has been apparent improvement in the mortality rate among wool and tannery workers due primarily to early diagnosis and specific chemotherapy[4, 65]

Clinical Aspects

There are two types of anthrax namely external anthrax (malignant carbuncle malignant edema) and internal anthrax (pulmonary and intestinal anthrax) which are generally recognized The fundamental pathological process however is quite uniform the result of infection being determined to some extent by the portal of entry the invasiveness of the strain and the resistance of the host As will be pointed out later external anthrax may terminate in fatal generalized malignant edema and anthracemia

Over 90 per cent of all anthrax infections take the form of the malignant carbuncle more commonly called the malignant pustule The latter term is actually a misnomer since there is little if any true pus in the typical cutaneous anthrax lesion unless secondary pyogenic infection becomes well established Lesions develop most often on the exposed areas of the body that is the extremities the face and the neck In many instances minimal trauma to the skin opens the way for the implantation of spores to initiate the process The earliest visible sign of infection to be noted in from one to three days after actual inoculation is a small red pruritic macule having the appearance of a flea bite In a few hours it enlarges taking on a fleshy yellow appearance Soon its top turns brown and it is often surrounded by a narrow ring of erythema On the second day a few fine glistening vesicles develop at

the periphery of the papule, and as these vesicles enlarge, the depressed center of the original papule ulcerates and turns dark brown and eventually, black The marginal vesicles at first small and filled with a clear yellow *gelatinous fluid rich in anthrax bacilli but poor in cellular content*, enlarge in a day or two and then become bluish red discharging a serosanguinous fluid On the 5th or 6th day the central ulcer is covered by a tough black and tenacious eschar which gradually extends into the crusting peripheral vesicles In many instances a wide area of erythema appears around the papule on the second or third day and non pitting brawny edema is a constant feature The typical cutaneous anthrax lesion is characteristically painless but the edema depending on its extent and location, may cause acute discomfort as will also the regional lymphadenopathy and lymphangitis which almost always develop The milder type of cutaneous infection localizes the edema gradually subsides and the black eschar drops off leaving a deep granulating crater which results in a heavy permanent scar If the eschar is forcibly removed prematurely that is while it is still adherent a new eschar will form on the granulating surface This second eschar will not have the deep black color of the original hemorrhagic scab Lesions on the neck and face usually are more severe and because of the great vascularity of the parts and the proximity to the vital circulatory junctions they carry a graver prognosis Multiple lesions on one or more extremities are not uncommon The lesion may take a week or ten days to develop and regress Transient bacteremia in the early stages is not unusual even in the relatively benign cases and it is thus not invariably a grave prognostic sign[49] Even in well localized cutaneous infections however there are often rather marked systemic signs and symptoms such as fever headache arthralgias and malaise

Malignant edema usually involves the loose connective tissue of the eyelids and the face the hands neck trunk and the mucous membranes It may start as a single vesicle or small group of vesicles but in many cases there appears to be no initial focus Instead of the formation of an eschar and relatively effective localization there is rapid spread of hemorrhagic edema following the lines of least resistance through the tissue planes There may be severe respiratory embarrassment due to cervical edema and widespread infiltration of the skin over the trunk Bacteremia is not uncommon under such circumstances in which it is usually a very grave prognostic sign Profound malaise circulatory collapse cyanosis and occasionally hypothermia indicate terminal generalization of the infection In rare instances the state of collapse has

been related to hemorrhage into the adrenal glands proven at autopsy as in the Waterhouse Friderichsen syndrome[9] It is thus obvious that the severe forms of external anthrax may terminate in internal or systemic anthrax with signs of pulmonary intestinal or central nervous system involvement

Pulmonary anthrax may result directly from the inhalation of spores in infected dust or wool containing dried blood from anthrax animals (woolsorters disease) The onset of symptoms is sudden with prostration fever chills pleuritic pain dyspnea and cough productive of bloody sputum containing anthrax bacilli The physical signs may not always indicate frank consolidation and roentgen examination may show only diffuse congestion Lobular pneumonia is encountered frequently at post mortem examination however There are often signs of pleural effusion The course of pulmonary anthrax consumes rarely more than 2 to 5 days and leads almost always to a fatal termination Inhalation anthrax may be manifest also by involvement at least initially of the nose and upper respiratory tract although generalized infection usually supervenes[11, 12, 13] It is apparent that in man the lungs serve as a portal of entry for invasion of the entire body by the anthrax bacillus and that in close analogy with experimental inhalation anthrax in animals pulmonary anthrax in most instances is not recognizable as a distinct pathological entity

Gastrointestinal anthrax may result either from actual ingestion of infected meat[14] or from oral infection complicating cutaneous or upper respiratory tract lesions[7] As already mentioned it may be the most prominent feature of a generalized infection terminating external anthrax of any type There is usually acute abdominal distress nausea vomiting bloody diarrhea and cramps Blood cultures are positive and anthrax bacilli are found in the stools and the vomitus A rapidly fatal outcome is the rule as in pulmonary anthrax and is preceded likewise by collapse delirium and unconsciousness However the occurrence of asymptomatic infection following the ingestion of infected meat has been reported[8] In these cases the presence of anthrax bacilli was indicated by a precipitin test using the patients serum containing anthrax antigen and standard anti anthrax serum This suggests that in man as in relatively resistant animal species the oral dose of spores necessary to cause overt infection is greater than the parenteral dose

As a secondary manifestation in about 5 per cent of the cases of either pulmonary or intestinal anthrax and occasionally without other localization there may be signs of meningeal and cerebral involvement

Symptoms of cerebral irritation may come on only a few hours before death and are most often nausea, vomiting, nuchal rigidity, delirium and convulsions. The cerebrospinal fluid may contain only bacilli with minimal cellular reaction or may be grossly bloody.[7] In rare instances meningitis may be the primary manifestation with no other obvious focus.[78]

Diagnosis

The diagnosis of cutaneous anthrax is almost always obvious from the appearance and evolution of the lesions as already described. A history of exposure to known sources, although often of helpful corroborative significance, is not always obtainable. This is especially true of the sporadic non-industrial cases. None of the usual serological tests are of any real value in practical diagnosis. The precipitin test mentioned earlier as having been evidence for latent infection is not constant enough to be of value where adequate control studies cannot be conducted.

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Treatment

Although widely practiced in the past, surgical intervention, either incision or attempts at excision of lesions, is condemned, especially now that relatively effective chemotherapeutic agents are available. The only conceivable indications for surgery might be for the relief of respiratory

obstruction during the course of extensive malignant edema Even in such cases respiratory embarrassment usually is due to generalized edema involving the entire respiratory tree rather than to localized obstruction which might be bypassed with tracheotomy

Until the advent of sulfonamides and antibiotics antianthrax serum was used widely in the treatment of anthrax infections with substantial evidence for its efficacy both in individual cases and in definite reduction of the overall mortality rate It is now no longer being produced commercially to any extent Arsenical preparations although of questionable benefit in experimental anthrax infections in animals[9] have been found to be as good as but no better than serum in the treatment of human infections[80] Neoarsphenamine however may in rare instance be indicated where sulfonamides or antibiotics are of no avail

Assessment of any chemotherapeutic agent in the treatment of human anthrax is limited by the fact that most cases treated and reported are of the cutaneous variety among which the recorded mortality even without treatment is not more than 5 to 15 per cent There are thus not many objective criteria other than mortality by which to judge the effect of therapy since most cutaneous lesions progress through the regular cycle of development which however may be definitely shortened by treatment Thus it has been noted that in some patients with malignant carbuncle[13] the edema remains unaffected by penicillin although the lesions may become sterile within 48 hours of the beginning of chemotherapy Such persistence of characteristic pathological changes suggests that the mechanisms responsible for the anthracoid lesion produced in animals by the inflammatory factor may be operative in human infections as well Claims for the rapid elimination of organisms from cutaneous lesions by chemotherapy must therefore be tempered with the realization that man is a relatively resistant host and that natural immune factors possibly also the same as those mentioned earlier as having a large part in determining the degree of animal susceptibility may play the larger role in controlling the infection

On the basis of in vitro studies as well as extensive experiments with highly susceptible animals in which mortality can be sharply reduced by chemotherapy and from the occasional dramatic response in individual human cases of anthrax it has become established that a number of *agents are of value in treating anthrax in man Thus sulfanilamide*[81] sulfapyridine[8] sulfathiazole and sulfadiazine[83] [81] have been found moderately effective in reducing the mortality of anthrax in mice guinea pigs and monkeys The last three compounds have been used with some

Symptoms of cerebral irritation may come on only a few hours before death and are most often nausea, vomiting, nuchal rigidity, delirium and convulsions. The cerebrospinal fluid may contain only bacilli with minimal cellular reaction or may be grossly bloody.[77] In rare instances meningitis may be the primary manifestation with no other obvious focus.[78]

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cillin when assayed under comparable conditions in reducing the mortality in experimental anthrax in mice[88]. This drug as yet has received little clinical trial in human anthrax, although one cure has been attributed to its use[89]. In one fatal case of malignant edema recently seen by this author, penicillin as well as streptomycin appeared to have not even a temporary influence on the course of the infection, although the strain isolated prior to therapy appeared to be sensitive to both antibiotics[100]. A similar case has been reported recently which ended fatally despite penicillin, streptomycin and sulfadiazine[101]. Though *B anthracis* is sensitive in vitro to chloromycetin in concentrations easily attainable with the usual therapeutic dosage, there has as yet been no recorded clinical experience with this or any of the other newer antibiotics.

From the data available to date it would appear that penicillin is the drug of choice in the treatment of any form of anthrax. The fact that all infections start as spore inoculations seems to make large doses of penicillin mandatory, of the order of 50 000 to 100 000 units every three hours, continuing until fever and local edema subside. This may take anywhere from three to four days to over a week. Any sign of meningeal involvement, such as headache, nuchal rigidity, Kernig's sign, photophobia or delirium, should be investigated with lumbar puncture and followed by the intrathecal instillation of penicillin. The absence of marked cellular reaction in the presence of *B anthracis* in the cerebrospinal fluid has been reported not infrequently, so that fluid from suspected cases should always be cultured and inoculated into mice. Penicillin should never be injected directly into cutaneous lesions as has been suggested by some, since any such mechanical interference, however minor, with the local process incurs the serious risk of spreading rather than retarding the progress of the infection.

If within 24 to 36 hours there is no discernible response as evidenced by either a fall in temperature or apparent arrest of the infection, streptomycin should be given in doses of 0.5 gm every 6 hours. The chief danger in using this antibiotic is the virtual certainty that the organism will become highly resistant within a short time, even if it has been shown to be relatively sensitive initially. No instance where streptomycin or penicillin resistance has developed during the course of treatment has come to the attention of this author to date, however. If there is still no improvement after 12 hours of streptomycin therapy and renal function appears still to be adequate, sulfadiazine may be given in full dosage either by mouth or intravenously as the sodium salt to attain blood levels of 10 to 15 mgm per cent.

evidence of success in human infections[6, 8] Until the wider application of penicillin to the problem of anthrax sulfadiazine and sulfathiazole were generally considered to be the drugs of choice They remain the second line of defense

In the original work on penicillin reported in 1929[86] *B anthracis* was found to be relatively susceptible to the action of penicillin in vitro In sufficiently high concentration it has been shown that germination of anthrax spores is inhibited in vitro by this antibiotic and that there is a bacteriostatic and bactericidal action on the vegetative cells[8] Penicillin has proved effective in reducing significantly the mortality in experimental anthrax in mice[88, 81] guinea pigs[93] and monkeys[94] The effect of penicillin is not enhanced in experimental anthrax infections by the concomitant use of antianthrax serum[91] The penicillins of choice in this infection appear to be X G and F, in the order named[9] *B anthracis* also has been shown to produce appreciable quantities of penicillinase[89, 93] which however does not appear necessarily to determine the sensitivity of a given strain to the action of penicillin at least under experimental conditions It is conceivable however that penicillinase produced either by the anthrax bacillus itself or by some other organism contaminating the anthrax lesion might have some retarding action on the curative effect of penicillin in human infections

Since the first reported clinical application of penicillin in human anthrax[94] this drug has had increasing use in various forms of infection with *B anthracis* but chiefly in treating cutaneous lesions The criteria for judging the efficacy of antibiotic therapy in the ordinary case of malignant carbuncle' have been the rapid subsidence of local edema prompt disappearance of organisms from the lesions and the relatively early involution of the latter[43] The pitfalls encumbering such deductions on purely clinical grounds have been pointed out already However it has been apparent in a few cases where bacteremia has been encountered and the systemic reaction has been severe that penicillin in all probability has prevented further spread of infection This has been particularly true of a few instances of malignant edema" where the prompt decline in fever and the abrupt clinical improvement have constituted striking clinical evidence of benefit from penicillin[9] Occasional cases with meningeal involvement and anthracemia also have been arrested by penicillin therapy[3, 97] A fatal outcome in a few cases despite penicillin argues for prompt institution of therapy before the lesions become too far advanced[17, 98]

Streptomycin has been found to be even more effective than peni

cillin when assayed under comparable conditions in reducing the mortality in experimental anthrax in mice[87] This drug as yet has received little clinical trial in human anthrax although one cure has been attributed to its use[89] In one fatal case of malignant edema recently seen by this author penicillin as well as streptomycin appeared to have not even a temporary influence on the course of the infection although the strain isolated prior to therapy appeared to be sensitive to both antibiotics[100] A similar case has been reported recently which ended fatally despite penicillin streptomycin and sulfadiazine[1 1] Though *B anthracis* is sensitive in vitro to chloromycetin in concentrations easily attainable with the usual therapeutic dosage there has as yet been no recorded clinical experience with this or any of the other newer antibiotics

From the data available to date it would appear that penicillin is the drug of choice in the treatment of any form of anthrax The fact that all infections start as spore inoculations seems to make large doses of penicillin mandatory of the order of 50 000 to 100 000 units every three hours continuing until fever and local edema subside This may take anywhere from three to four days to over a week Any sign of meningeal involvement such as headache nuchal rigidity Kernig s sign photophobia or delirium should be investigated with lumbar puncture and followed by the intrathecal instillation of penicillin The absence of marked cellular reaction in the presence of *B anthracis* in the cerebrospinal fluid has been reported not infrequently so that fluid from suspected cases should always be cultured and inoculated into mice Penicillin should never be injected directly into cutaneous lesions as has been suggested by some since any such mechanical interference however minor with the local process incurs the serious risk of spreading rather than retarding the progress of the infection

If within 24 to 36 hours there is no discernible response as evidenced by either a fall in temperature or apparent arrest of the infection streptomycin should be given in doses of 0 5 gm every 6 hours The chief danger in using this antibiotic is the virtual certainty that the organism will become highly resistant within a short time even if it has been shown to be relatively sensitive initially No instance where streptomycin or penicillin resistance has developed during the course of treatment has come to the attention of this author to date however If there is still no improvement after 12 hours of streptomycin therapy and renal function appears still to be adequate sulfadiazine may be given in full dosage either by mouth or intravenously as the sodium salt to attain blood levels of 10 to 15 mgm per cent

It will be apparent that it is of the utmost importance to determine the sensitivity of the individual strain of *B anthracis* to penicillin strepto mycin and sulfadiazine prior to treatment and to retest the sensitivity at intervals during treatment, if cultures of the blood and lesions continue positive This is advocated despite the occasional observation of good chemotherapeutic results in patients with anthrax from whom strains of *B anthracis* relatively resistant to penicillin were isolated[10] If there appears still to be no clinical response and there is marked resistance of the strain in vitro to antibiotics and sulfonamides neoarsphenamine in one or more intravenous doses of 0 6 to 9 09 gm is definitely indicated Contaminating organisms are encountered occasionally *Staphylococcus aureus* being the one most frequently isolated Secondary infection with Friedlander's bacillus responding to streptomycin where penicillin had failed has been reported recently[10]

Supportive measures in anthrax are of extreme importance Respiratory embarrassment should be carefully watched for in cases of pulmonary anthrax or of malignant edema of the trunk involving the neck Oxygen should be used freely to relieve dyspnea and fluid should be administered intravenously not by clysis in quantities commensurate with fever and urinary output Renal shutdown may be encountered in severely toxic patients and excess fluids administered intravenously may do more harm than good The hemorrhagic tendency although usually a terminal manifestation can be combatted with transfusions of fresh whole blood

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CHAPTER XI

BOTULISM

By Ernest C Dickson

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Introduction

Botulism is a type of food poisoning which is caused by a specific bacterial toxin and which is characterized by delayed onset and involvement of the nervous system associated with disturbances of vision difficulty in swallowing and in talking persistent constipation extreme weakness subnormal temperature and a rapid pulse The mortality in the United States is very high

The word botulism is derived from *botulus* meaning a sausage and in the early German literature was used synonymously with *Wurstvergiftung* or sausage poisoning Later it was found that the characteristic symptom complex of botulism may follow the ingestion of other types of preserved meats smoked ham or bacon pickled fish etc so that in more recent German literature the term is used to include meat poisoning and fish poisoning

The cause of the intoxication was discovered by van Ermengem[1, 2] in Belgium in 1894 Van Ermengem demonstrated that the victims in an outbreak at Ellezelles were poisoned by a toxin in pickled ham and that the toxin was produced by the growth of a large anaerobic spore bearing bacillus which he called Bacillus botulinus He also showed that the bacteria themselves would not cause the death of laboratory animals but that it was the toxin elaborated during their growth in the food and ingested with it which produced the illness

This toxin is extremely virulent for various types of animals as well as for man

Within recent years there have been a number of outbreaks of food poisoning of this type in the United States in which not only human beings but also domestic fowl and domestic animals were poisoned. The majority of outbreaks in which human beings were affected were caused by the ingestion of canned vegetables or fruits in which Bacillus botulinus had grown and produced its toxin[4] most of those in which domestic fowl were poisoned were caused by discarded spoiled canned food which had been prepared for human consumption and practically all those affecting domestic animals were caused by infected fodder or silage[5, 6, 7]

The term botulism therefore has now a much wider application than when it was first employed and includes all cases of poisoning with the botulinus toxin regardless of the type of food in which it may have developed or of whether human beings or animals or fowl are the victims

Bacillus Botulinus and Its Toxin

Despite the mass of information concerning botulism which has been accumulated during the past few years there is still much difference of opinion as to many of the differential points in cultural characteristics of the organism. However the morphology and the grosser cultural characteristics have been established and the action of the toxin upon laboratory animals is characteristic and easily demonstrated and verified by the use of specific antitoxins. The methods by which the presence of the organism or its toxin may be identified in suspected foods have been described by several authors[8, 9, 10] and are easily followed although the isolation of the organizm in pure culture is more difficult

The organism is a large bacillus measuring from 2 to 6 microns in length by from 0 5 to 1 2 microns in width and having slightly rounded ends. The bacilli may arrange themselves in pairs end to end or in unfavorable environment in chains. Under suitable conditions they readily form spores which are oval and usually situated near the end of the bacillus producing a tennis racquet appearance although in some instances they may be more centrally placed and form spindles. The bacilli are slightly motile and have from four to eight flagella arranged around the periphery. They stain readily by the ordinary methods and by Gram s method but are likely to be mottled or granular if left too long in the alcohol

Bacillus botulinus has usually been described as a strict anaerobe but recent investigations[11] have shown that it will thrive in about two thirds of atmospheric oxygen. It grows well in symbiosis with certain aerobic bacteria and there is no difficulty in obtaining vigorous growth with active toxin formation

in brain beef or beef heart medium in open tubes of standard size In broth cultures which exceed four inches in depth there is no necessity of stratifying the broth with oil or petrolatum

The reaction of the medium plays an important part in the growth of Bacillus botulinus Dozier[11] found that the range of growth in peptone solution lies between PH 4 5 and PH 9 but other authors have reported growth in medium of PH 11 Meyer[8] found that a reaction of PH 8 4 was optimum for the recovery of the organism from field materials such as soil hay vegetables etc and in the Stanford laboratory[12] it was found that peptic digest broth adjusted to PH 7 0 to 7 5 was entirely satisfactory for the rapid growth of pure cultures

The earlier European investigators recorded that the optimum temperature for the growth of Bacillus botulinus lay between 20 and 30 degrees Centigrade but different observers in the United States have found that the majority of the strains if not all which have been isolated in this country produce more rapid growth and as virulent a toxin at 37 degrees Centigrade The greater part of the recent work in this country has been done at the latter temperature

The appearance of the culture is fairly characteristic In glucose broth there is a diffuse cloudy growth within 24 hours at 37 5 degrees C and within 48 hours at 28 degrees C but the bacteria soon settle to the bottom of the tube leaving the medium clear In glucose gelatin plates in an oxygen free atmosphere the young colonies appear as transparent pale yellow spherules which are surrounded by a zone of liquefaction As they grow older the transparency is lost the colonies become opaque darker in color and nodular in appearance The gelatin liquifies rapidly and the bacteria collect in flakes at the bottom of the plate In deep agar cultures the upper limit of growth is about one centimeter below the surface of the medium and the young colonies are oval or kidney shaped disks which are translucent and nucleated the nucleus being near the indented margin

In beef infusion 2 per cent deep agar there is often a peculiar vacuolated appearance of the colony[7] but in liver agar of equal strength the vacuolization is less constant Hall[1] reports that the form of the colonies in deep agar varies with the consistency of the agar The older colonies may show a tufted outgrowth from the region of the nucleus and occasionally may have an irregular shaggy appearance

The majority of authors agree that the organism is proteolytic and produces a peculiar cheese like odor In litmus milk there is precipitation of a finely divided coagulum and slow peptonization of the precipitate and according to Hall[14] all strains which were examined by him fermented glucose glycerol and salicin but did not ferment lactose saccharose or inulin None of Hall s strains produced indol

Sporulation varies in various strains but usually occurs within a few days

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Bacillus botulinus has usually been described as a strict anaerobe but recent investigations[11] have shown that it will thrive in about two-thirds of atmospheric oxygen It grows well in symbiosis with certain aerobic bacteria and there is no difficulty in obtaining vigorous growth with active toxin formation

the dried form is very stable The toxin is rapidly destroyed by heat boiling for from seven to ten minutes being sufficient to detoxify cultures or infected food materials which are extremely toxic

According to van Ermengem[2] the addition of o per cent by volume of normal soda solution will destroy the toxin within a short time but an equal volume of normal hydrochloric acid will not affect it Bronfenbrenner and Schlesinger[7] found that in laboratory tests acidification with hydrochloric acid to the degree found normally in the stomach contents will greatly increase the virulence but Geiger and Gouwens[2] have been unable to confirm this observation

Van Ermengem[2] reported that the toxin is precipitated by tannin alcohol and neutral salts Bronfenbrenner and Schlesinger[22] have confirmed his observations with alcohol and salts Putrefaction of the material in which the toxin has formed does not affect its virulence in fact in certain vegetables and fruits for example in olives spoilage of the product appears to increase the ease with which the growth of Bacillus botulinus and its toxin formation may occur Under ordinary conditions the presence of other bacteria in a mixed culture does not affect toxin formation although Hall and Peterson[3] have shown that the presence of certain acid forming aerobes may inhibit it to a certain extent in glucose broth

It was formerly believed that Bacillus botulinus could not grow and produce a virulent toxin except in the presence of protein of animal origin but observations made in the Stanford laboratories[1] have shown that this is not correct The organism thrives and produces virulent toxin in mediums prepared from many vegetables and fruits and its presence in canned vegetables and fruits has been responsible for about two-third of the outbreaks of human botulism which have been recorded in the United States[4]

The virulence of the toxin varies with different strains and under different conditions of growth In the Stanford Laboratory series of strains the maximum virulence of toxin obtained in a standard medium varied betwen that represented by the minimum lethal dose for a guinea pig of 0 005 and 0 000 05 cc respectively but Bengston[1] obtained a more virulent toxin M L D 0 000 01 cc in the medium adopted as standard by the Hygienic Laboratory of the U S Public Health Service In preserved foods the virulence is not usually so great as may be obtained under laboratory conditions but there are numbers of instances recorded in which there was sufficient toxin in cans of spoiled home-canned string beans and asparagus to cause the fatal poisoning of persons who merely tasted the contents of the containers In one such instance the toxicity in string beans was such that the M L D for a guinea pig was 0 000 5 cc and in another the toxicity in asparagus was M L D 0 000 1 cc[4]

The mechanism whereby the botulinus toxin gains entrance into the body and its fate after it has been absorbed are not fully understood Church[14] reports that sufficient toxin may gain entrance through abrasions in the alveolar

in brain or beef heart medium and although it may be somewhat delayed is also profuse in glucose peptic digest liver broth containing 1 per cent glucose and in vegetable juices enriched with gelatin Recent observations at Stanford University[13] have shown that the normal botulinus spores possess a characteristic which is typical of certain leguminous seeds viz , that a certain percentage of them may remain dormant for several months in an environment which is optimum for the growth of the majority and that when these dormant spores eventually germinate they produce as vigorous growth and as virulent toxin as those which germinate more promptly

Extensive investigations in several laboratories[12, 14, 17] have shown that some of the botulinus spores are extremely resistant to heat Under the conditions of the laboratory experiments the majority of the spores are easily and quickly destroyed by exposure to the temperature of boiling water but some of them will survive exposure to that temperature for six hours to the temperature of five pounds steam pressure (107 5 degrees Cent) for forty five minutes to the temperature of ten pounds steam pressure (115 degrees Cent) for ten minutes and to the temperature of fifteen pounds steam pressure (121 degrees Cent) for six minutes If a thin layer of oil is placed upon the surface of the medium in which the spores are heated they will survive for a much longer time for instance they may resist exposure to the temperature of fifteen pounds steam pressure for twenty two minutes a fact which is of much importance in connection with the processing of certain types of foods

The heat resistance of the spores is maximum when they are heated in media of approximately neutral reaction and rapidly becomes less when the medium is more acid or more alkaline The reaction of the medium is not the only factor which determines this variation however since in different vegetable juices of approximately the same reaction the resistance of the spores may vary considerably

A much longer dormancy has been observed in spores which have survived exposure to heat, than in normal spores but it has not been determined whether this is due directly to the effect of the heat or whether the spores which survived the heat did so because of some characteristic which would also have made them dormant When spores which have been heated germinate they produce a vigorous growth and a virulent toxin

Botulinus toxin is a true exotoxin and differs from other bacterial toxins in that it is not destroyed by the action of the gastric secretions The chemical constitution is not known but Bronfenbrenner and Schlesinger[18] believe that the molecule must be very small and of a comparatively simple structure The toxin can be precipitated from the broth in which it was formed by saturation with ammonium sulphate and obtained in powdered form In broth it is relatively unstable if exposed to air or to bright light but if kept cool in a sealed tube and in the dark it deteriorates very slowly Bengston[19] reports that

types of Bacillus botulinus in Europe each of which produce a specific toxin which is neutralized only by the homologous antitoxin In 1917 Dickson and Howitt[3] found that there are also two distinct types of Bacillus botulinus among the strains which have been isolated in the United States These were called Types A and B respectively Recently Bengston[33] has described as another type of Bacillus botulinus a strain which was first described by Saunders[34] She has called this Type C A few tests of strains of Bacillus botulinus which were obtained from Germany show that serologically they are identical with our Type B but there are no records as to whether the second type described by Leuchs[26], the Darmstadt strain corresponds to our Type A or Bengston s Type C The majority of the human outbreaks of botulism in the United States have been caused by Type A but a few have been caused by Type B There is no record of the occurrence of human outbreaks caused by spoiled food containing Type C

All investigators agree that complete protection may be afforded if sufficient homologous antitoxin is administered at the time the botulinus toxin is injected or if it is given before the toxin but if the antitoxin is to be of any value as a therapeutic measure it must be administered within a comparatively short time after ingestion of the toxin before the clinical signs of the intoxication have become apparent

Experiments in the Stanford Laboratory indicate that the length of time which may elapse between the administration of toxin and the injection of the antitoxin depends in part upon the amount of toxin which has been taken into the body as there is no doubt that after massive doses of toxin the latent or incubation period is materially shorter than after small amounts and that the antitoxin is of little value after the affected animals have developed symptom Clinically in this country there has been no well established instance in which the administration of antitoxin after development of symptoms has been of any value[4]

Distribution of Bacillus Botulinus and Source of Poisoning

As was stated above all the strains of Bacillus botulinus with but three exceptions which have been recovered from foods that were responsible for outbreaks of botulism in Europe were obtained from foods of meat or fish origin The greatest number of cases have been observed in Germany but outbreaks have also been reported in Russia Austria Hungary Switzerland Denmark Holland Belgium France and England

In the United States from 1889 to 1922 inclusive there have been at least 118 recorded outbreaks of botulism affecting human beings and at least 100 more in which domestic fowl or animals were poisoned by eating discarded spoiled preserved vegetables or fruits which had been prepared for human con

mucus membrane or through cuts or bruises in the skin to cause fatal poisoning and Bronfenbrenner and Schlesinger[25] believe that it may be absorbed directly through the stomach The last named authors[26] have also shown that purified toxin which is as toxic by subcutaneous injection as is the crude material is much less toxic than the crude toxin when administered by mouth and they conclude that some substance is removed by purification which aids in the absorption through the gastro-intestinal tract Several authors[27, 28, 29] have reported that the toxin may be demonstrated in the blood serum of victims of the intoxication for several days after ingestion of the toxin but there is no record that it has been demonstrated in any of the secretions

There is comparatively little reaction sometimes slight local hyperaemia at the site of subcutaneous injection of the toxin and there are no characteristic local lesions in the mucous membranes of the gastro intestinal tract when the toxin is ingested Kempner and Schepilewsky[30] showed that it may be in part neutralized when mixed with central nervous system tissue but this effect is not a specific one since cholesterol lecethin tyrosene butter and emulsified oils have a similar effect

Van Ermengem[2] demonstrated that symptoms of poisoning appear in animals more quickly after intravenous injection than after subcutaneous or intraperitoneal injection or after ingestion and various authors have shown that there is a definite relationship between the duration of the interval before symptoms appear and the amount of toxin administered but regardless of the amount of toxin and of the method by which it gains access to the body there is always a delay before the appearance of symptoms which may be compared to the incubation time of acute infections Many animals and fowl as well as human beings[4] are susceptible to poisoning from ingestion of the toxin but it always requires much more toxin according to Bronfenbrenner and Schlesinger[31] one thousand times as much as by intraperitoneal injection to produce poisoning in this manner

Different investigators[32, 33, 34] in the United States have shown that under certain laboratory conditions it is possible to demonstrate that detoxified botulinus spores may germinate and grow within the animal body and produce sufficient toxin to cause fatal botulism In order to accomplish this result it is necessary to administer enormous numbers of spores many times as many as could be ingested under ordinary circumstances in spoiled food and the result has not been demonstrated when animals ingested spores in the numbers which may be found in spoiled food There is no record that such a true infection with Bacillus botulinus has ever occurred in human beings and it is highly probable that the formation of botulinus toxin within the body does not play any important part in human botulism

In 1897 Kempner[35] demonstrated that a potent botulinus antitoxin may be produced in goats and in 1910 Leuchs[36] showed that there are at least two

Commercially prepared foods are somewhat protected because there are several stages in the progress from producer to consumer during which spoilage may be recognized and the spoiled food may be discarded and because the consumer is much more critical in her attitude towards spoiled commercially prepared foods. Moreover the commercial canning industry is alert to the possibility of botulinus contamination of preserved foods and has adopted methods of preservation and processing some of them under state supervision[4] which ensure destruction of any botulinus spores which may have been placed in the containers with the raw material.

In preserved food which contains botulinus toxin there is almost always some sign of spoilage which should warn the one who prepares the food that it is unfit for consumption although if the bacteria are present in pure culture there may be little if any softening or discoloration of the product. The absence of a vacuum within the container or the escape of gas when the container is opened should always arouse suspicion.

Bacillus botulinus produces a peculiar rancid odor not unlike that of strong cheese which is usually apparent when the container is first opened although sometimes it is masked and does not become noticeable until the food is heated. There have been a few instances[4] in which the food showed no visible signs of spoilage and had no recognized unusual odor when the container was opened. Upon several occasions the person who opened the container smelled and tasted the food and concluded that it was not spoiled although her subsequent illness and the demonstration of toxin in the food proved that she had been mistaken and in several instances those who ate the poisonous food as salad did not recognize any unusual taste or odor because they were masked by the salad dressing.

The fact that botulinus toxin may produce a characteristic symptom-complex in chickens and turkeys[5] was ascertained during the investigation of outbreaks of human botulism in California in which remnants of the poisonous food had been discarded. The chickens usually become ill within from twelve to eighteen hours after ingestion of the toxin and die in from twenty four to forty-eight hours. The illness in fowl has been described as limber neck but preferably should be called fowl botulism.

Buckley and Shippen demonstrated that symptoms which are identical with those produced by forage poisoning in horses and mules may be experimentally produced by feeding the toxin of Bacillus botulinus and Graham and his associates[6] and Rusk and Grindley[7] have recorded outbreaks of forage poisoning in which the illness was shown to be due to botulinus toxin. In California a survey of the distribution of forage poisoning in horses was made by Geiger[4] who found that there is an interesting geographical relationship of the distribution of botulism in human beings and domestic fowl suggesting

sumption In addition to these there have been many instances in which domestic animals were poisoned by eating spoiled ensilage or fodder and there is evidence that at least some of these were victims of true botulism

Prior to 1914 the diagnosis of botulism was based entirely upon clinical observations but since that time there have been many instances[4] in which the clinical diagnosis was confirmed by the demonstration of botulinus toxin in the food or by the isolation of Bacillus botulinus from the food from the faeces of the victims or from tissues obtained at necropsy In a series of 82 human outbreaks in which the responsible food was known Bacillus botulinus or botulinus toxin was demonstrated in laboratory tests in 30 and chickens or animals died after eating discarded remnants of the food in 16 more

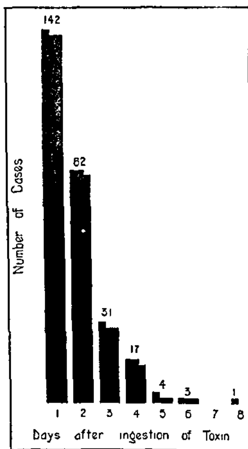


CHART I Showing time of onset of symptoms in days after ingestion of toxin in 280 cases

Among the foods which have been responsible for 98 outbreaks of human botulism in the United States home canned products have been responsible for 67 and commercially prepared foods have caused 31 String beans have caused the most outbreaks 25 corn has caused 16 spinach 11 olives 10 asparagus 7 beets and apricots each 3 and pears 2 Details of the causes of the poisoning are shown in Chart I

The most difficult problem in the control of botulism arises from the fact that in home canning processes the temperature of boiling water is the maximum which is available in most instances although there is the additional factor that housewives will often attempt to use spoiled home canned products whereas they will return spoiled commercially canned products to their grocer The danger is greatest in foods which are served as relishes salads or dessert without being cooked after they are removed from the containers but the habit of tasting preserved foods to determine whether they are spoiled is also unsafe and there are records of nearly a score of instances in which women have been poisoned in this manner

3 The characteristic growth in broth cultures with the production of a virulent toxin which can be demonstrated by inoculation of susceptible animals and controlled by specific antitoxic sera

Where the original suspected food or the container from which it was taken is available small portions of the juice or of the washings should be injected into guinea pigs subcutaneously for demonstration of the toxin and in case the animals show symptoms of botulinus poisoning further tests should be made with specific antitoxins A and B for more complete indentification

SYMPTOMATOLOGY AND COURSE

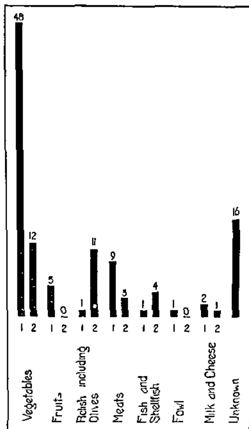


CHART 2 Showing the reported causes of 114 outbreaks of Botulism in the United States
1 Home canned products
2 Commercially canned products

The onset of the typical symptoms of botulism in human beings is usually from eighteen to thirty six hours after the ingestion of the toxin although in rare instances they may appear as early as twelve hours and in a few instances they may not be noted for from forty eight hours to several days after the poisonous food is eaten (Chart II) In about one third of the cases observed in the United States there have been manifestations of acute gastro intestinal disturbances varying from a sense of burning and discomfort in the region of the stomach to severe gastro enteritis with nausea vomiting and diarrhoea When such acute disturbances occur they usually begin soon after the spoiled food is eaten and may subside within a few hours but more often they persist until they are replaced by the typical botulinus symptoms It is probable that they are not de

that at least a part of the forage poisoning in California may be botulism

Recent investigations have shown that Bacillus botulinus is widely distributed in nature Mrs Burke[42] succeeded in isolating the organism from mouldy bird pecked cherries which were offered for sale in the open market and from beans bean leaves and a spider which were taken from a plot of ground in which had been grown beans that were infected with Bacillus botulinus Meyer and Dubovsky[43] found that the organism is widely distributed in virgin soil in soil from gardens cultivated fields etc in vegetables and fruits which were purchased in the open market and in hay straw and other animal fodder In a series of 624 specimens collected from 36 counties in California they obtained approximately 30 per cent of toxic cultures and in 1538 examinations of materials collected from all the states of the Union with the exception of Virginia[44] there was an average of 24 3 per cent of toxic cultures The only states from which the specimens failed to show some toxic cultures were Arizona New Mexico South Dakota and Rhode Island and from some of these states only a very few specimens were examined

As a result of their investigations these authors concluded that Bacillus botulinus is a common soil anaerobe of the Western States of the Cordilleran system that it is less frequently encountered in the Atlantic States and that it is relatively rare in the Middle States the Great Plains and the Mississippi valley that Bacillus botulinus spores are far more prevalent in virgin and in pasture soils than in dirt soil or manure collected from animal corrals pig pens etc and that string bean pods and leaves ensilage and decayed vegetation yield a relatively high percentage of positive cultures They also note that human and animal botulism is not infrequent in those states in which Bacillus botulinus Type A predominates or in which the percentage of positive cultures exceeds 20 to 30 per cent

Method of Demonstrating Bacillus Botulinus in Suspected Material

The methods to be employed for examining materials which are suspected of being responsible for the poisoning in the various outbreaks of botulism have been described in detail elsewhere[8] The points considered most essential for identification are

1 The demonstration of large Gram positive bacilli with rounded ends and subterminal spores

2 The occurrence of anaerobic growth of characteristic appearance in glucose infusion agar cylinders with formation of gas and fragmentation of the medium

The difficulty in swallowing is apparently largely due to impaired function of the pharyngeal muscles as the patients state that they have difficulty in forcing the food from the pharynx into the oesophagus but that if it is once started they can easily swallow It is probable however that the dryness of the mouth and throat is a contributing factor as in the milder cases the patients are able to swallow solid food if they take a drink of liquid Attempts to swallow often induce strangling spells which may be very severe and may persist until the patient is exhausted Regurgitation of fluids through the nose and insufflation into the trachea and bronchi frequently occur during the strangling spells

A sensation of muscular weakness is an early manifestation of botulism and progressive weakness which is especially noticeable in the muscles of the neck and of the extremities is characteristic of the intoxication Quite early in the course of the illness there may be incoordination of muscular movements causing ataxic gait and inability to pick up small objects the patients may complain that they are unable to masticate their food because of weakness of the jaws and continued effort of any kind causes extreme fatigue In the typical severe case the patient lies helpless in bed with the muscles relaxed in a manner not unlike that seen in deep general anaesthesia but although the condition may be so severe as to simulate paralysis it is characteristic that the deep reflexes are intact and that the patient may be able to initiate effective muscular contraction to open the eyes or to raise the head or an extremity once or twice although he can neither maintain the muscular effort nor repeat it

It is characteristic of botulism that there is almost complete absence of sensory disturbance There may be initial headache and gastric distress but usually the patient does not suffer any pain Occasionally there is tinnitus and partial deafness and a few cases have been reported in which there was numbness and tingling of the extremeties but in by far the greater number of reported cases it is noted that there was no disturbance of sensation

Mentality usually remains clear until within a very short time before death Restlessness insomnia and occasionally hysterical attacks may be observed particularly at the onset but the patient often becomes apathetic or even somnolent as the intoxication progresses There may be spells of irritability when he is aroused apparently induced by his inability to make himself understood or to swallow *and often there is great apprehension of approaching dissolution* Occasionally there is coma for a short time before death and a few cases are recorded in which there were convulsions but a most striking feature of the intoxication is that mentality is usually unimpaired throughout the illness Inhibition of many of the secretions is also characteristic of botulism and the patients complain bitterly of dryness of the mouth pharynx and nasal passages It has been reported that at times there may be an increase in sali

pendent upon the action of the botulinus toxin per se but are caused by the local irritation produced by the spoiled food in which the toxin is carried into the stomach

The typical case of botulism differs from one of the usual type of food infection in that there are no acute gastro intestinal disturbances A characteristic feature of the intoxication is the early inhibition of gastro intestinal movements with the result that constipation sets in early and is extremely persistent The constipation may be present from the onset of symptoms or may develop after a period of purging Frequently there is distension of the intestines and occasionally the patients complain of colic in the early stages but there is rarely any abdominal tenderness or rigidity

The earliest symptom in the majority of cases is a peculiar indefinite lassitude and fatigue sometimes associated with dizziness or headache and when acute gastro intestinal disturbances are not present the patient usually attributes his condition to the accompanying constipation

Disturbances of vision occur very early and may be the first indication that the patient is seriously ill There may be early scintillations and dimness of vision due to a loss of ability to accommodate for near vision, and diplopia mydriasis loss of light reflex and blepharoptosis are practically constant Occasionally the pupils are unequal and irregular in contour and when the dilated pupil is not covered by the drooping upper lid there may be photophobia Complete loss of accommodation soon follows

Imbalance of the extrinsic muscles of the eyes is responsible for the early diplopia and for nystagmus which may be unilateral Occasionally these muscles seem to lose all power and the eyeballs remain immobile and fixed in the sockets In some instances the patients complain of vertigo

The majority of authors agree that there is never true blindness although Saint Martin[65] found congestion of the vessels of the retinal papillae and contraction of the visual fields in several patients Apparently the dimness of vision is dependent upon loss of ability to accommodate for near vision since usually the patients can distinctly see distant objects with either eye alone

Coincidently with or closely following the onset of visual disturbances there is usually difficulty in swallowing and in talking and frequently the patients complain of a sensation of constriction of the throat The tongue appears to be larger than usual is sluggish in its movements and heavily coated on the surface although the edges may be clean

The difficulty in pronouncing words is apparently chiefly due to the impaired motility of the tongue although fatigue of the laryngeal muscles is also an important factor The voice is low and without normal tone and eventually there is complete aphonia Even in the milder cases the onset of early fatigue is very evident and after short attempts at conversation speech becomes noticeably slower and more difficult and the voice more husky

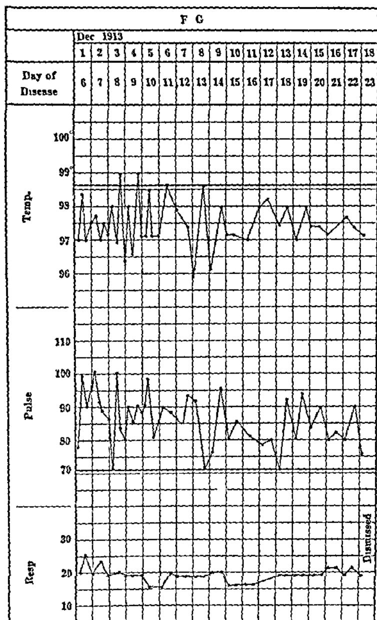


CHART 3 Clinical chart of case of Botulism

vary secretion in animals but in our experience this has not been noted in human victims the rule being that there is a marked diminution of the serous portions of the saliva although the mucus of the whole gastro intestinal tract is secreted in a thick glairy form which is removed with the greatest difficulty One of the most distressing features of the intoxication is the accumulation of thick mucus in the pharynx and it is probable that the lack of serous secretion in the mouth is largely responsible for the impairment of the sense of taste According to the literature there is usually inhibition of sweat secretion but in the group of cases reported in this country it has not been uncommon to find the patient bathed in a profuse sweat which had an offensive odor When sweating is inhibited the skin becomes hard and dry

There is considerable variation in the reports concerning the secretion of urine but apparently in the majority of cases the amount of urine secreted depends directly upon the amount of fluid which the patient receive Oliguria and anuria have been described but that is not surprising when one considers the difficulty or impossibility of swallowing liquids There is apparently no characteristic change in the urinary constituents or sediment

The temperature is usually subnormal (Charts III and IV) In the majority of ca es it ranges between 96 and 98 6 degrees Fahrenheit and in uncomplicated cases remains low during the whole illness Not infrequently there may be fever during the last days of the intoxication but this is usually a sign of the development of bronchopneumonia

The pulse rate may be slow in the early stages of the intoxication but later in the course of the illness it becomes rapid It is not uncommon to observe a pulse rate of from 100 to 120 per minute and in some cases as much as 150 or 160 per minute (Charts III and IV) The action of the heart muscle is impaired there may be no visible cardiac impulse and the heart sounds are feeble and distant The combination of subnormal temperature and rapid pulse is most striking

There is often no disturbance of respiration in the early stages of the intoxication but towards the end breathing becomes difficult and labored and there may be extreme dyspnoea and irregular breathing sometimes of the Cheyne Stokes type with all the accessory muscles brought into play Later as fatigue of the respiratory mechanism develops there may be partial or complete asphyxia and the most frequent immediate cause of death is respiratory failure

The data concerning the results of the usual clinical laboratory tests in botulinus intoxication are very incomplete As was stated above examination of the urine shows no characteristic changes from the normal Blood counts have been made in a few cases without revealing any typical blood picture In a series of eight patients the red blood cell count was between 5 200 000 and 5 600 000 per cubic millimeter and in forty four cases the leucocyte counts lay between 5 000 and 20 400 per cubic millimeter In one series of twenty

nine cases[4] it is recorded that differential counts yielded a normal formula as a rule and in the whole series of forty four there were only two instances in which the polymorphonuclear count was more than 85 per cent In at least one case in which the leucocyte count was above 16 000 necropsy revealed extensive bronchopneumonia

Examination of the cerebrospinal fluid has been recorded in four cases In one instance it was stated that there were 80 cells per cubic millimeter but the type of cells was not specified In the remainder the fluid was reported normal

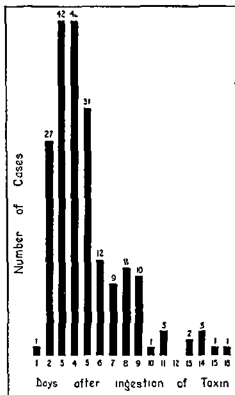


CHART 5 Showing the time of death in days after ingestion of toxin in 196 fatal cases

Blood pressure records in twenty two cases showed systolic pressures of from 105 to 150 mm of mercury and diastolic pressures of from 70 to 100 mm In the younger patients the pressure showed no variations from normal and in every instance where a high reading was obtained there was evidence that it was caused by disturbances which antedated the intoxication

The duration of the illness varies greatly A few of the fatal cases may terminate within forty eight hours after the poisonous food is ingested but as was noted by Muller[7] the majority of persons die in from four to eight days after the fatal meal and few die who have survived for more than ten days The duration of the illness of 196 fatal cases which occurred in the United States is shown in Chart V

Death usually occurs from cardiac or respiratory failure It has been frequently observed that the heart continued to beat for several minutes after respiration had ceased and cases are recorded where artificial respiration has maintained life for several hours after voluntary respiration had ceased Usually there is terminal asphyxia with cyanosis and occasionally the patient dies in a strangling spell It is not uncommon that although there may be an apparent improvement in the general condition of the patient death results from insufflation bronchopneumonia

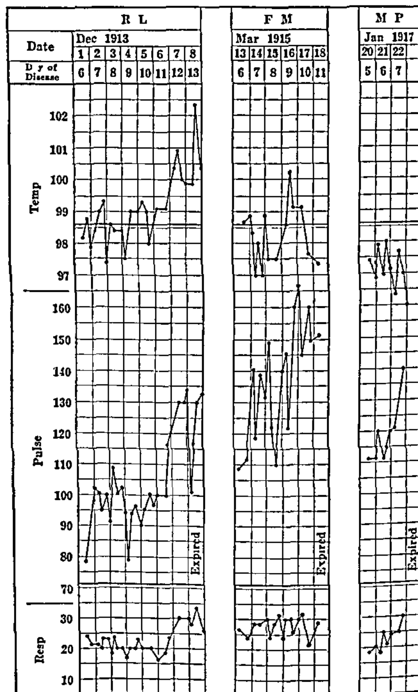


CHART 4 Clinical charts of fatal cases of Botulism

In the central nervous system the meninges at the base of the brain especially around the pons and medulla are usually more congested than at the cortex and the basilar sinuses are usually engorged with blood There may be multiple hemorrhages in the meninges especially around the base of the brain and the upper part of the cord The brain tissue is congested and may be edematous and show hemorrhages

The lungs are extremely hyperaemic and may show areas of collapse and hemorrhages Bronchopneumonia is extremely common The heart muscle may be flabby and opaque and there may be ecchymoses in the pericardium endocardium and pleura The vessels of the mesentery are engorged and the intestines are hyperemic and often show hemorrhagic areas The liver and kidneys are usually cloudy and hyperemic and a considerable amount of blood escapes when the liver is sectioned The spleen may be large and engorged and may contain multiple hemorrhages There is rarely any excess of fluid in the pleural or peritoneal cavities

Microscopic examination of the tissues show that congestion is general and extreme the veins are practically all engorged with blood the capillaries are distended and many small arteries remain filled The greatest engorgement in the spleen occurs in the medullary veins and in the liver in the intralobular veins and adjoining capillaries The liver cells show varying degrees of parenchymatous degeneration of the cells Sections of the kidney show marked parenchymatous degeneration of the convoluted tubules which may be necrotic and desquammated The straight tubules contain debris and granular casts Occasionally the glomerular tufts are engorged with blood and in several animals and one human case in our series there was an accumulation of exudate containing red blood cells in the glomerular clefts Sections of the lungs show marked congestion often exudate and hemorrhage and frequently bronchopneumonia Sections of the brain show numerous minute hemorrhages around the distended veins in the meninges and brain tissue often without any apparent break in the contour of the vessel wall and in the brain as in the other organs there are often large hemorrhages which are not apparently located in the immediate vicinity of any of the larger vessels In a few cases there is an excessive number of leuocytes in the blood within the vessel and in the hemorrhagic areas but there is never perivascular infiltration with lymphocytes such as is characteristic of epidemic encephalitis

Warthin[40] has described the formation of gas bubbles in the brains of victims of botulism which he believes to be due to the reaction to local infection with Bacillus botulinus but this has not been observed in our series of human victims nor in a large series of animals in which the poisoning was experimentally produced

A peculiar type of thrombi which are rich in polymorphonuclear leucocytes was first described by Ophuls[41] and occurs in the majority of human

When recovery occurs convalescence is extremely slow and tedious The severity of the illness usually reaches its maximum within ten days of the poisoning and improvement follows slowly The strangling and the difficulty in speaking and swallowing frequently improve first, but the muscular weakness and disturbances of vision disappear more slowly Many cases are recorded in which the patients were comparatively well within two or three months but the weakness vertigo and emaciation may persist much longer The disturbances of vision appear to be the last to clear up and may persist for months Insofar as can be ascertained there appears to be no permanent severe disability although some patients complain of constipation following recovery

Morbidity and Mortality

The morbidity rate of botulinus intoxication has been very low but seems to be steadily increasing Bitter[48] has recently reported that there have been at least seventy outbreaks of botulism in Prussia since 1897 and that the number is increasing from year to year In the United States the condition was not recognized before 1889 but since that time there have been more than two hundred outbreaks in which human beings or domestic animals or fowl were poisoned by eating food which had been prepared for human consumption in addition to the not inconsiderable number of outbreaks of forage poisoning in domestic animals in which the poisoning was due to infected fodder or silage

The recorded mortality of botulism in the United States has been much higher than in Germany where all outbreaks must be reported to the health authorities In Mayer s[49] series of 812 cases collected from the official records in Germany the mortality was 44 9 per cent but in Bitter s[48] series of 302 cases it was only 16 8 per cent In the United States during the period from 1889 to 1922 inclusive there have been at least 411 persons poisoned with botulinus toxin of whom 268 died a case mortality rate of 65 2 per cent It is probable that this mortality rate is too high because it was obtained from outbreaks which were so severe as to attract public attention but it is significant that in Germany the highest mortality has been observed in outbreaks which were caused by spoiled canned vegetables and that in the United States the majority of outbreaks have been caused by preserved vegetables

Pathology and Pharmacology

The only constant finding on macroscopic examination of the bodies of victims of botulinus intoxication is the marked congestion of the central nervous system and of the abdominal and thoracic viscera

to repeated stimulations of normal intensity however there is in botulism animals a rapid development of fatigue manifested by an increase in the intensity of stimulus necessary to induce physiologic muscular contraction and resulting in the diminished tonus of the skeletal muscles and the extreme weakness which are characteristic of the intoxication

In the somatic as in the parasympathetic system the effect of the toxin is in the nerve endings and is not an organic destruction of tissue but it has not been determined whether the damaging influence is exerted upon the anatomical nerve endings or upon the myoneural junction

Diagnosis

In the early stages of botulinus poisoning when about one third of the victims show signs of acute gastro intestinal disturbance with nausea vomiting pains in the abdomen and diarrhoea it is not possible to make a definite diagnosis of the intoxication In group outbreaks there is usually indication that some form of food poisoning is responsible but differentiation between bacterial food infection of the Bacillus paratyphosus Bacillus enteritidis type of bacteria and botulism may be extremely difficult A careful survey of the probable cause of poisoning may give a clue bacterial food infection is usually transmitted by infected fresh food more often of animal origin which does not show signs of spoilage whereas botulism is always caused by uncooked or imperfectly cooked preserved food which usually shows more or less marked spoilage Moreover the continued absence of fever should suggest that bacterial food infection is not the cause and should lead one to think of botulism The onset of disturbances of vision blurring or double vision or blepharoptosis in such cases will usually confirm the diagnosis

When single cases occur the problem is still more difficult The sudden onset of nausea and vomiting associated with pains in the abdomen and diarrhoea occurring within a few hours after a meal is not pathognomonic of food poisoning Any acute abdominal condition appendicitis cholecystitis cholelithiasis gastric ulcer etc certain chest conditions such as pleurisy and angina pectoris and many acute infectious diseases may produce symptoms of a similar nature Here again however the absence of fever and of leucocytosis should attract attention and suggest that botulinus intoxication may be at fault

In rural districts it sometimes happens that chickens or other domestic fowl develop signs of limber neck after eating discarded food which may have been thrown out because it was spoiled Should this occur it should always cause one to think of the possibility of botulism and to ascertain whether any human beings have been exposed to the poisoning

cases and in animals which have survived experimental intoxication for more than forty eight hours[1] These thrombi may be widely distributed throughout the body occurring in the blood vessels of the abdominal and thoracic viscera as well as in those of the central nervous system but recent observations have shown that they are not pathognomonic of botulism[52] There is no evidence that they have any causal relationship to the clinical manifestations of the intoxication

Observations in this country have failed to confirm the reported findings of Marinesco[53] and other European investigators of the occurrence of damage to the Nissl granules of the ganglion cells of the brains and cords of animals and human beings who succumbed to botulinus poisoning and it is impossible to explain the characteristic signs and symptoms of botulism on the basis of such pathology

In 1877 Purckhauer[54] expressed the belief that the poisonous substance which causes botulism exerts its influence peripherally upon the muscles and not centrally upon the nervous mechanism which controls the muscles and recent observations in Germany and in the United States suggest that he was probably correct insofar as he attributed the disturbances of function to peripheral damage Schubel[55] working with frogs and certain invertebrate forms Edmunds and Long[29] working with frogs guinea pigs rabbits dogs cats and chickens and Dickson and Shevky[56] working with rabbits cats and dogs all found that the characteristic action of the botulinus toxin is peripheral and not central but whereas Schubel and Edmunds and Long believe that the effect is curare like in nature the work at Stanford University failed to show any curare like action

The results of the experiments of Dickson and Shevky may be summarized as follows

Botulinus toxin does not directly damage the protoplasm of muscle cells nor does it cause any interference with the conduction of initial nerve impulses from the cerebral cortex to the voluntary muscles

The most striking effect of the toxin is the production of a peripheral blocking of nerve impulses of normal intensity in the nerves of the parasympathetic system This block results in the loss of physiologic response in the involuntary muscles and glands which are supplied by the parasympathetic nerves but may be temporarily overcome by the administration of stimulations of much greater intensity than normal showing that it is not due to any organic break in continuity of the conducting mechanism

In botulism animals that show extreme symptoms and signs of poisoning, there is no impairment of the physiologic response of the voluntary muscles to initial normal stimulation of the nerves supplying them and the reflex motor response as well as the reflex vasomotor response to peripheral stimulation is unimpaired When the nerves supplying the voluntary muscles are exposed

portions of the food show signs of illness In either ca e all persons who may have eaten any portion of the suspected food should be given full do es of antitoxin

It should be remembered that there are at least two types of Bacillus botulinus Types A and B which have been shown to be responsible for human outbreaks of botulism in the United States and possibly also a third Bengston s Type C although this strain has not as yet been proved to have been the cause of toxin production in preserved foods It is necessary therefore unless the type of toxin which is responsible for a given outbreak has been identified to administer a polyvalent antitoxin or preferably a mixture of the various types of antitoxin each of which is of known potency

Because the poisoning in botulism is caused by a given amount of toxin which is ingested as such with the food and is not elaborated by the growth of Bacillus botulinus within the body it is advisable to administer the antitoxin in a single large dose 20 000 units intravenously rather than to give it in repeated injections of small amounts The usual precautions for the administration of horse serum should be observed and the patient should be desensitized if necessary before the injection is made

After the early administration of botulinus antitoxin the most important thing in the treatment of botulism is that the patient be put to bed and kept as quiet as possible preferably by himself in a darkened room from which all unnecessary visitors are excluded Experiments have shown that fatigue and not paralysis is responsible for the disturbances of mu cular function and tha it is fatigue of the respiratory mechanism or of the heart which is responsible for death Restlessness and insomnia may be controlled by bromides if the patient is able to swallow or by morphine without atropin by subcutaneous injection Bronfenbrenner and Weiss suggest that the patient should be kept under morphine during the whole course of the intoxication but care must be taken not to give sufficient morphine to depress the respiratory function

If the patient is seen early before the difficulty in swallowing and the strangling spells are severe the stomach should be thoroughly washed out to remove all remnants of the poisonous meal even if the patient has been vomiting and full doses of magnesium sulphate or oleum ricini should be placed in the stomach before the tube is withdrawn In severe cases however it is doubtful whether the benefit to be derived from washing the stomach is sufficient to offset the fatigue which the manipulation induces and there is always the danger of bringing on strangling spells from which the patient may not recover

It is not advisable to attempt to empty the stomach by the administration of apomorphine or by other emetics if the patient is suffering from strangling spells becau e of the danger of insufflation bronchopneumonia

The colon should be flushed with high enemeta even if there has been diar

The condition which most closely resembles botulism is belladonna poisoning but this can usually be distinguished by the excitement and delirium which is characteristic of it and which is not observed in botulism Epidemic encephalitis cerebrospinal syphilis acute poliomyelitis various types of bulbar paralysis and toxic ophthalmoplegias must also be differentiated but can usually be excluded by taking a careful history and by the course of the disease and the results of clinical laboratory tests

It has been recorded by several authors that botulinus toxin may be demonstrated by injecting white mice with blood serum from the victims of the poisoning Edmunds and Long[25] have shown that this is true in dogs which were experimentally poisoned but it is not always true of human victims of botulism A negative test does not exclude the possibility that the illness is due to botulism

The demonstration of hyperemia and of the characteristic thrombi in the blood vessels of the tissues obtained at necropsy add further evidence that botulinus intoxication was responsible for the death of the patient although the presence of the thrombi is not pathognomonic of botulism Demonstration of the toxin in the suspected food or recovery of Bacillus botulinus from food or from the intestinal contents or the spleen of the victim establishes the diagnosis

Treatment

The treatment of botulism is most unsatisfactory and there has been no material improvement in the methods of treatment since the etiology of the poisoning was established The therapeutic use of botulinus antitoxin has been disappointing although in laboratory tests it is possible to protect animals if the antitoxin is administered soon after the injection of the toxin in the interim before symptoms of poisoning appear The antitoxin does not protect if it is withheld until after symptoms have developed

In the human outbreaks of botulism in the United States[4] with but one exception[46] botulinus antitoxin was never administered until after the development of severe symptoms and there is nothing in the clinical records of the patients to indicate that the course of the intoxication was in any way affected by it

From our present knowledge it would seem that botulinus antitoxin may be of therapeutic value if it can be administered before the onset of clinical symptoms of botulism and there are at least two circumstances in which this may be possible In large group outbreaks of botulism it always happens that one or more patients develop symptoms before the others and in rural districts domestic fowl which develop limber neck after eating discarded remnants may become ill and even die before the human victims who have eaten

spores It is impossible to recognize the presence of the spores on raw food material excepting by bacteriologic examinations which are impracticable where quantities of food are being prepared Poisoning has never been observed clinically except after the ingestion of uncooked or imperfectly cooked preserved food in which the toxin has been formed before the food was eaten As some of the processes employed in preserving food and particularly is this true of processes employed in the home will not destroy the spores of Bacillus botulinus if they happen to be present in the raw material the possibility of botulinus contamination of preserved foods must be kept in mind

There is always more or less marked evidence of spoilage in food which is contaminated with botulinus toxin but in some instances there may be no signs of putrefaction The typical butyric acid or cheese like odor can usually be detected at once but occasionally it is in some way masked when the jar is first opened and may escape notice In many cases there is undoubted evidence of fermentation of the contents of the container which may be shown by the bulging of the ends of a tin container by signs of leakage around the covers of bottled goods or by an escape of gas under pressure when the container is opened

It is unusual that poisoning of human beings occurs from food which is obviously spoiled although domestic animal or fowl may be poisoned by eating such food that has been discarded It should be remembered however that in many cases the appearance of the food may be very nearly normal and that unless the person who opened the container is on the alert the presence of an unusual odor may escape notice Where poisonous food is served with mayonnaise or other salad dressing the odor or even the taste may be completely masked

The toxin is destroyed by boiling for from five to seven minute and it has repeatedly been shown that food which in its uncooked state has caused poisoning has failed to cause illness after it was cooked It i probably on this account that the number of outbreaks of poisoning has not been larger since in all the recorded cases of poisoning from canned foods in thi country the food has either been served without further cooking after it was removed from the can as salad dessert or relish or has been tasted by the one who opened the container to determine whether it was good If all preserved food were boiled before it was eaten or even tasted there would be no further cases of botulinus intoxication

It has been said that the use of alcoholic drinks with meals will offer some protection against botulinus poisoning but it is doubtful whether this i true In one outbreak of poisoning the toxin was contained in home brew liquor which contained 15 per cent alcohol yet five per ons were poisoned and four of them died (4)

rhoea and it is advisable to give frequent high soapsuds enemata unless the procedure causes too much fatigue Sometimes evacuation of the bowels may be induced by pituitrin

Simple nourishing food should be given if the patient can swallow or will tolerate the stomach tube without a struggle but care must be taken to avoid anything which will fatigue the patient or induce strangling spells Liquids should be given freely retention enemata or the Murphy drip being well tolerated because of the inactivity of the intestine

Supporting treatment may be applied as indicated Strychnin was recommended by Muller[47] and appears to be of some benefit It should be given in as full doses as can be tolerated without muscular twitching especial care being exercised if the patient is also receiving morphine Cardiac distress may be combated with caffeine or with some hypodermic preparation of digitalis but as the cardiac distress is usually terminal one can expect but little benefit from their use Atropin should never be administered in botulism because in many ways it accentuates the disturbances in function which the toxin produces

The accumulation of thick mucus in the pharynx is one of the most distressing features in botulism and is responsible for much annoyance and fatigue as well as for inducing strangling spells The mucus should be removed by an attendant as often as is necessary to relieve the patient by wiping with a soft swab on a spatula or the handle of a teaspoon or by gentle suction from an aspirating bottle through a soft catheter Pilocarpine has been used to increase salivary secretion and prevent the accumulation of thick mucus but it must be used with care because of the danger of pulmonary edema

Death usually occurs from respiratory failure and cases are recorded in which the heart action has persisted for a considerable time after voluntary respiration had ceased Oxygen should be administered when evidences of asphyxia become apparent and artificial respiration with a pulmotor if possible should be begun if the respiratory movements fail and should be continued as long as the heart continues to beat Edmunds and Long[29] report that botulism dogs have been kept alive for thirty hours after voluntary respiration ceased and there is always a possibility that life may be maintained until the effect of the toxin is exhausted

Convalescence is extremely slow and tedious but recovery is usually complete As soon as the patient is able to swallow he should be given nourishing food and such tonic treatment and exercise as is indicated General weakness including cardiac irritability may persist for several weeks or months and the patient must be warned against the danger of overexertion

PROPHYLAXIS

Bacillus botulinus is widely distributed in the soil and raw food materials particularly vegetables and fruits are often contaminated with botulinus

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The prevention of Botulismus therefore lies not in curtailing the use of preserved food but in recognizing that no food which shows the slightest sign of variation from normal should be eaten or even tasted and also incidently that it should not be placed where domestic animals or fowl can gain access to it unless it has been thoroughly boiled A further safeguard is afforded if all preserved food is boiled before it is eaten and it should be borne in mind that there are few if any of the ready to use canned foods which are in any way damaged by being thoroughly boiled and cooled before they are served

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CHAPTER XI-A

FOOD-BORNE DISEASE
Food Infections and Food Poisoning

By VLADO A. GETTING

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A vast variety of diseases may be transmitted through the medium of food, milk or water. Typhoid fever, paratyphoid fever, botulism and dysentery are classic examples of bacterial diseases that are transmitted to the unsuspecting consumer through the food and drink he ingests. In a food-borne disease the etiological agent gains entrance to the body through the alimentary tract. Formerly the term food poisoning has been applied conventionally to any acute gastroenteritis characterized by nausea, vomiting and diarrhea. However, a

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Symptomatology

In food infections the incubation period varies from six hours to two weeks with characteristic averages for the different types of organism The shortest periods are encountered with salmonella infections but usually the incubation period of a food infection is longer than that of food poisoning Whereas fever is a common symptom of food borne infections it is not a frequent finding in staphylococcal enterotoxic poisoning Nausea vomiting abdominal cramps or pain and diarrhea leading to prostration are the usual rapid sequence in severe staphylococcal poisoning chills sweats and toxemia are other frequent symptoms *The duration of illness is usually a matter of hours and recovery is rapid* In salmonella infection recovery is a matter of days and in typhoid weeks In the investigation of any suspected food borne outbreak an analysis of the symptoms often will give the epidemiologist a clue to the etiological agent The shortest incubation periods are observed in some types of chemical food poisoning where symptoms may occur in ten minutes to several hours The enterotoxin of *Staphylococcus aureus* produces symptoms in two to six hours whereas salmonella infection incubation averages six to twenty four hours Nausea or vomiting is not likely to occur in food infections with long incubation periods

Modes of Contamination of Food

Having obtained a record of the symptoms of all the patients in a given outbreak the next most important step is to obtain a dietary history from each As soon as the investigator finds which foods are common to all cases steps should be taken to prevent further cases by stopping the further use of these foods Thereafter a study of the vehicle can be made determining its source handling storage and preparation in an endeavor to ascertain the mode whereby the food became contaminated Lastly the etiological agent is determined by laboratory examination of the food and of the vomitus and feces of patients and food handlers A complete investigation can reconstruct the epidemic step by step from its source to the time of the investigation

Food borne infection may be due to animal disease transmitted through milk, milk products or meat directly to the consumer Trichiniasis is a classic example of animal disease transmitted through uncooked pork Brucella and certain salmonella and streptococcal infections are examples of bacterial diseases of animals transmitted to man Food may on the other hand be contaminated by flies rats or mice or by food handlers who are active cases or carriers and who soil their hands with saliva urine or feces thereby introducing the organisms into the food which they handle Infection of food with staphylococci and strepto

substantial portion of so called food poisoning is not poisoning but an infection and this term is therefore, erroneous Ptomaine poisoning is another misleading term often applied to an acute gastroenteritis As a matter of fact ptomaine poisoning does not exist Ptomaines are substances produced in the decomposition of food by bacteria Examples of this type of decomposition are the ripening of game and wild fowl and the aging of cheese None of these foods all of which are relatively high in ptomaines, is poisonous

Classification of Food borne Diseases

The food borne diseases can be divided into two main groups (1) food infection in which the etiological agent is a living organism and the symptoms are the manifestation of the reaction of the host to the action of the organism and (2) food poisoning in which the causative agent is a noxious substance that in itself is responsible for the characteristic clinical sequence with or without the presence of a living organism

The etiological agent of food infection may be a virus a bacterium, a protozoan or a helminth By far the commonest agents are bacteria, chiefly the Salmonella and the Shigella Trichiniasis is perhaps the most prevalent type of helminth food infection and amebiasis the commonest protozoan infection An example of virus food borne infection is infectious diarrhea of the newborn The following food infections are reviewed in this chapter amebiasis, trichiniasis typhoid fever paratyphoid fever bacillary dysentery, undulant fever, scarlet fever and septic sore throat

Food poisons may be subdivided into two groups (1) endogenous poisons which usually are present in the food e g mushroom poisoning or oxalate poisoning from rhubarb leaves and (2) exogenous poisons which are not an integral part of the food but an addition to it

The exogenous poison may be an organic substance such as the alkaloid derived from a flagellate which at certain times of the year infests mussels the toxin of *Clostridium botulinum* or the commonest type of food poison the enterotoxin of a hemolytic *Staphylococcus aureus* Poisoning from this group often is termed food intoxication since the symptoms are usually due to a toxin On the other hand the exogenous poison may be an inorganic compound such as the residue of an insecticide spray on fruits or vegetables the accidental addition of fluorine to food or the solution of cadmium from replated metal containers This type of food poisoning often is called chemical poisoning The types of food poisoning to be reviewed in the paragraphs under the heading Food Poisoning are staphylococcal enterotoxic poisoning botulism shellfish and chemical poisoning

of known milk borne outbreaks in the United States increased from an average of 17 per year prior to 1923 to an average of 42 per year since that date From 1938 to 1941 inclusive (Table I) there were 163 outbreaks with 6 923 cases and 48 deaths

TABLE I

Disease Outbreaks Conveyed through Milk and Milk Products in the United States 1938–1941

Disease	No of Outbreaks	No of Cases	No of Deaths
Diphtheria	2	36	3
Dysentery	9	813	0
Food poisoning			
Staphylococcal	5	868	0
Other	22	522	0
Gastroenteritis	13	1,326	0
Paratyphoid fever	2	24	0
Scarlet fever	11	187	1
Septic sore throat	18	2 512	12
Typhoid fever	50	4 8	32
Undulant fever	8	119	0
Unknown	3	38	0
Totals	163	69 3	48

* Assembled from data collected by the United States Public Health Service

Raw milk and raw milk products or pasteurized milk improperly handled were responsible for most of the outbreaks The known responsible diseases in order of number of cases were septic sore throat gastroenteritis staphylococcal food poisoning undulant fever diphtheria and paratyphoid fever

In upstate New York from 1917 to 1941 there were 168 milk borne outbreaks with 9 982 cases of which 6 812 were septic sore throat and scarlet fever 1 4 3 gastroenteritis 1 209 typhoid or paratyphoid fever 411 bacillary dysentery 123 diphtheria and 4 poliomyelitis In Massachusetts from 1933 to 1940 there were 6 milk borne outbreaks with 469 cases Four outbreaks were of scarlet fever or septic sore throat (412 cases) 2 of undulant fever (12 cases) and 1 of gastroenteritis (35 cases) This is the smallest number of outbreaks recorded for any similar period in Massachusetts In 1931 65 per cent of the population of Massachusetts lived in communities with regulations requiring the pasteurization or certification of milk By 1940 80 per cent of the population were living in these communities and over 90 per cent of the milk consumed in Massachusetts was pasteurized Undoubtedly this increase in pasteurization is responsible for the decrease of outbreaks of milk borne disease

cocci may occur from boils infected wounds or sore throats of food handlers The storage of food is an important factor in the morbidity rate, the longer the infected food is kept in a warm place, the higher the attack rate Vegetables may be infected with amebas by fertilizing the soil with human excreta Botulism is caused by undestroyed spores of *Clostridium botulinum* derived from the soil

Chemicals may gain entrance to foods An insecticide spray may be found on fruits or vegetables roach powder, which contains fluorine, may be added to the food by mistake for flour or milk powder or a solution in an acid medium of cadmium from replated food containers may contaminate their contents Often the mode of infection of the food cannot be determined Many food processing methods may be the means of introducing pathogenic organisms unless proper precautions are taken Some of the outbreaks reviewed here illustrate the protean modes whereby food becomes the vehicle of food borne disease

Prevalence of Food borne Disease

The serious nature of gastroenteritis in military forces can be estimated from the incidence of this disease in the United States Army During World War I, according to Dunham[1], 87 774 cases of enterocolitis and diarrhea were admitted to hospitals with 195 deaths an annual case rate of 21 ·6 per 1,000 men Undoubtedly there were many more cases that did not require hospitalization The average time lost from duty was 11 days a total of almost 1,000,000 days in hospitalized cases alone In 1934 and 1935 the rates of hospital admissions were 21 95 and 21 14 per 1 000 respectively

Rodenwaldt states dysentery is the most dangerous of war diseases not only because of its physical effects but also because it has such a powerful demoralizing effect During World War I there were 155 000 cases of dysentery in the German Army During the invasion of Poland in September, 1939 several outbreaks of bacillary dysentery occurred simultaneously These outbreaks were due to different organisms and were therefore, unconnected The speed of the campaign forced troops to eat whatever they could lay their hands on, including a great deal of unripe fruit, and the heat made them drink water regardless of its purity Strangely there was no epidemic among the Polish prisoners or the civilian population Many German troops had to be evacuated to the rear, where, because of unfavorable conditions and overcrowding dysentery spread among the hospital personnel

However food borne disease is prevalent in peacetime as well as wartime In 1923 the United States Public Health Service began the collection of data on milk borne disease[3] Prior to this date knowledge of milk borne outbreaks was limited to those reported in the literature As shown by these surveys the number

of known milk borne outbreaks in the United States increased from an average of 17 per year prior to 1923 to an average of 42 per year since that date From 1938 to 1941 inclusive (Table I) there were 163 outbreaks with 6 923 cases and 48 deaths

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* Assembled from data collected by the United States Public Health Service

Raw milk and raw milk products or pasteurized milk improperly handled were responsible for most of the outbreaks The known responsible diseases in order of number of cases were septic sore throat gastroenteritis staphylococcal food poisoning undulant fever diphtheria and paratyphoid fever

In upstate New York from 1917 to 1941 there were 168 milk borne outbreaks with 9 982 cases of which 6 812 were septic sore throat and scarlet fever 1 423 gastroenteritis 1 209 typhoid or paratyphoid fever 411 bacillary dysentery 123 diphtheria and 4 poliomyelitis In Massachusetts from 1933 to 1940 there were 6 milk borne outbreaks with 469 cases Four outbreaks were of scarlet fever or septic sore throat (412 cases) 2 of undulant fever (12 cases) and 1 of gastroenteritis (35 cases) This is the smallest number of outbreaks recorded for any similar period in Massachusetts In 1931 65 per cent of the population of Massachusetts lived in communities with regulations requiring the pasteurization or certification of milk By 1940 80 per cent of the population were living in these communities and over 90 per cent of the milk consumed in Massachusetts was pasteurized Undoubtedly this increase in pasteurization is responsible for the decrease of outbreaks of milk borne disease

In 1938 the United States Public Health Service began the collection of data on outbreaks conveyed through foods other than milk and milk products. From 1938 to 1941 (Table II) there were 656 food borne outbreaks with 17,529 cases and 120 deaths. The commonest diseases in order of numerical importance

TABLE II

DISEASE OUTBREAKS CONVEYED THROUGH FOODS OTHER THAN MILK AND MILK PRODUCTS IN THE UNITED STATES 1938–1941

Disease	No of Outbreaks	No of Cases	No of Deaths
Botulism	25	64	33
Chemical poisoning	7	87	14
Dysentery	16	1,038	3
Food poisoning			
Staphylococcal	208	4,865	6
Other	229	6,096	7
Gastroenteritis	75	3,845	4
Paratyphoid fever (Salmonella infection)	14	475	1
Streptococcal infection	1	40	0
Trichiniasis	30	246	14
Typhoid fever	46	578	37
Miscellaneous	5	195	1
Totals	656	17,529	120

were food poisoning other than staphylococcal, staphylococcal food poisoning, gastroenteritis, dysentery, typhoid fever, paratyphoid fever and other salmonella infections, trichiniasis, chemical poisoning, botulism and streptococcal infection.

The responsible vehicles (Table III), are correlated with the type of disease. Canned foods were the sole vehicle for botulism. Dysentery was transmitted most frequently by salads, soups and an unrecognized food, unrecognized perhaps owing to a longer incubation period. Chemical poisoning was conveyed by various foods including puddings. Food poisoning other than staphylococcal, staphylococcal food poisoning and gastroenteritis were transmitted by nearly all types of foods, the most important for the first two being pastries and ham, and for the third pastries and meats other than ham and pork. Paratyphoid fever was carried chiefly by stuffing, fish, poultry and salads, scarlet fever by ham, trichiniasis by pork and typhoid fever by pork products, fish, poultry and salads. Pastry was responsible for more outbreaks of most diseases than any other known single food; usually it was filled with cream or custard.

The annual increase in the number of recorded outbreaks is due in part to better reporting. As yet there are several states that are not reporting food borne disease. Three states reported over half of the outbreaks in 1939. This

TABLE III

DISEASE OUTBREAKS CONVEYED THROUGH FOODS IN THE UNITED STATES RELATION BETWEEN TYPE OF FOOD AND DISEASE

Food	Botulism		Dysentery		Chemical Poisoning		Food Poisoning Other than Staphylococcal		Staphylococcal Poisoning		Gastroenteritis		Paratyphoid Fever		Scarlet Fever		Trichinasis		Typhoid Fever		Other	
	o	c	o	c	o	c	o	c	o	c	o	c	o	c	o	c	o	c	o	c	o	c	o	c
Canned food																								
Commercial	2	5	–	–	–	–	1	3	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Home	23	59	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Dressing (stuffing)	–	–	–	–	–	–	3	215	2	128	1	9	1	7	–	–	–	–	–	–	–	–	–	–
Fish	–	–	–	–	–	–	14	551	2	20	12	568	1	11	–	–	–	–	4	31	–	–	–	–
Gravies etc	–	–	–	–	–	–	3	66	4	143	4	75		–	–	–		–	–	–	–	–	–	–
Pork products																								
Ham	–	–	–	–	–	–	27	26	46	1273	5	102	–	–	1	96	1	7	–	–	2	15		
Other	–	–	–	–	–	–	16	389	9	38	3	108	–	–	–	–	27	232	4	61	–	–		
Meat other than pork products	–	–	–		–	–	22	603	12	522	13	1367	–	–	–	–	1	5	1	12	–	–		
Poultry	–	–	–	–	–	–	30	1270	8	284	5	92	1	21	–	–	–	–	4	7	–	–		
Pastries	–	–	–	–	–	–	46	360	75	1,563	16	311	–	–	–	–	–	–	1	56	2	49		
Puddings etc	–	–	–	–	2	3	2	73	1	52	3	33		–	–	–	–	–	–	–	–	–		
Salads	–		3	181	–		18	811	9	315	6	121	1	50	–	–	–	–	2	62	3	65		
Sandwiches	–	–	–	–	–	–	12	76	10	579	4	116	–	–	–	–	–	–	1	21	–	–		
Soup	–	–	1	6	–	–	4	122	1	3	–	–	–	–	–	–	–	–	–	–	–	–		
Miscellaneous	–	–		–	5	73	11	320	4	77	2	12	–	–	–	–	–	–	14	149	–	–		
Unknown	–	–	1	8 1	1	10	33	600	2	49	12	910	4	305	1	27	–	–	14	100	–	–		
Totals	25	64	16	1038	8	156	242	5 5	185	4968	6	3974	8	394	2	123	29	244	45	569	7	129		

o = number of outbreaks c = number of cases

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The annual increase in the number of recorded outbreaks is due in part to better reporting As yet there are several states that are not reporting food borne disease Three states reported over half of the outbreaks in 1939 This

TABLE III

Disease Outbreaks Conveyed through Foods in the United States. Relation between Type of Food and Disease

Food	Botulism		Dysentery		Chemical Poisoning		Food Poisoning Other than Staphylococcal		Staphylococcal Poisoning		Gastroenteritis		Paratyphoid Fever		Scarlet Fever		Trichinosis		Typhoid Fever		Other	
	o	c	o	c	o	c	o	c	o	c	o	c	o	c	o	c	o	c	o	c	o	c
Canned food																						
Commercial	2	5	–	–	–	–	1	3	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Home	23	59	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Dressing (stuffing)	–	–	–	–	–	–	3	215	2	128	1	9	1	7	–	–	–	–	–	–	–	–
Fish	–	–	–	–	–	–	14	551	2	20	12	568	1	11	–	–	–	–	4	31	–	–
Gravies, etc.	–	–	–	–	–	–	3	[illegible]	4	143	4	75	–	–	–	–	–	–	–	–	–	–
Pork products																						
Ham	–	–	–	–	–	–	27	[illegible]	46	1273	5	102	–	–	1	96	1		–	–	2	15
Other	–	–		–	–	–	16	359	9	38	3	108	–	–	–	–	27	232	4	61	–	–
Meat, other than pork products	–	–	–		–	–	22	603	12	522	13	1367	–	–	–	–	1	5	1	12	–	–
Poultry	–	–	–	–	–	–	30	1270	8	284	5	92	1	21	–	–	–	–	4	77	–	–
Pastries	–	–	–	–	–	–	46	360	75	1365	16	311	–	–	–	–	–	–	1	50	2	49
Puddings, etc.	–	–	–	–	2	73	2	73	1	52	3	33	–	–	–	–	–	–	–	–	–	–
Salads	–	–	3	181	–	–	18	811	9	315	6	121	1	50	–	–	–	–	2	62	3	65
Sandwiches	–		–	–	–	–	12	[illegible]	10	579	4	116	–	–	–	–	–	–	1	21	–	–
Soup	–	–	1	[illegible]	–	–	4	122	1	23	–	–	–	–	–	–	–	–	–	–	–	–
Miscellaneous	–	–	–	–	5	73	11	320	4	177	2	12	–	–	–	–	–	–	14	140	–	–
Unknown	–	–	12	851	1	10	33	600	2	49	12	970	4	305	1	27	–	–	14	100	–	–
Totals	25	64	16	1038	8	156	242	5775	185	4068	86	3974	8	394	2	123	29	244	45	569	7	129

o = number of outbreaks c = number of cases

difference in reporting is not a true indication of the actual prevalence of food borne disease The states that reported large numbers of outbreaks are equipped with active epidemiologic units and have made more complete studies

An analysis of the prevalence of outbreaks for 1938 to 1941 inclusive reveals that food is a far more prolific source of food borne disease than is milk alone Of 112 outbreaks in 1938 70 (61 per cent) were spread by a food other than milk, and in 1939 the number was 148 (78 per cent) of 189 outbreaks Food other than milk was the vehicle in 218 (84 per cent) of 260 in 1940 and 223 (85 per cent) of 26? in 1941 Of the 823 outbreaks in the entire period 80 per cent were transmitted by a food vehicle other than milk and only 20 per cent by milk or a milk product Moreover in 1938 and 1939 food borne outbreaks were more numerous than water borne Fuchs recording 91 water borne outbreaks as compared with 301 where the vehicle was food

A further example of the prevalence of food borne disease is furnished by data from Worcester Massachusetts During 1941 2 outbreaks were recorded In 1942 when the Worcester Department of Public Health became especially interested in food borne disease there were 11 outbreaks with 230 cases Undoubtedly there were other outbreaks that were not brought to the attention of the department Assuming that the prevalence of food borne disease is the same in the remainder of Massachusetts and in the United States as it is in Worcester, there should have been reported a total of 247 outbreaks in Massachusetts and over 7 000 in the United States In short food borne disease is more prevalent than is indicated by the reports of health departments

Food Infection

Amebiasis

Since the Chicago outbreak in 1933 amebic dysentery has ceased to be regarded as a tropical disease There is no doubt that this disease is more prevalent in the tropics than elsewhere as shown by its spread through food handlers among the Americans stationed at Aruba in the Caribbean Schoenleber[4] found that the stools of over 25 per cent of the men were positive for amebas after several years of residence An amebic colitis rate of 36 8 per 1 000 per annum was reached Examination of the stools of food handlers revealed that 33 per cent were carriers Active control of food handlers resulted in a 50 per cent reduction in the incidence of amebiasis after one year and 92 per cent after three years The control of food handlers consisted of the examination of the stools of all new employees those with amebas in their stools were rejected Stool examinations were reported every month and if amebas were found the person was

removed from duty treated with a course of carbarsone or yatren and returned to duty when three successive stool examinations were negative Strict hand washing and fingernail cleaning routines were instituted Examination of Italian prisoners from Africa by British Army physicians revealed that asymptomatic carriers of *Shigella dysenteriae* and of *Endamoeba histolytica* cysts were potential sources of epidemics among prisoners Four carriers who had no symptoms and no recurrence for three to fifteen months were carriers of the former and two of these were also carriers of the latter

The Chicago outbreak was the first recognized epidemic of the disease in a civilian population in the United States At first the investigators believed that it was due to a high carrier rate among the food handlers of the hotels that were the focus of the epidemic Of 364 food handlers examined in September 1933 11 were carriers and 15 were active cases In October the food handlers and other employees were re examined There were newly positive stools in 60 of the food handlers and in 100 of 498 other employees Twenty three additional carriers were found by culturing the stools Because the 1 400 patients in the two hotels subsequently returned to their homes cases were scattered among the residents of forty three states three Canadian provinces and the Territory of Hawaii On their return home 40 per cent of the patients were subjected to operation because the illness was mistaken for appendicitis The mortality rate among all the cases was only 7 per cent

Subsequent investigation revealed that the epidemic was due to infected drinking water Through faulty plumbing fresh sewage from another hotel was introduced directly into the drinking water supply of the two hotels Chlorination was sufficient to kill the pathogenic bacteria but was not effective against the amebas which are more resistant to chlorine

In 1935 there occurred another Chicago water borne outbreak of amebic dysentery among firemen and spectators who drank from a heavily contaminated auxiliary water supply used to extinguish an extensive stockyard fire occurring in that city

McCoy of the United States Public Health Service states in the World War bacillary and amebic infections occurred side by side in some military units and occasionally in the same person The sources of infection were a human carrier or case a contaminated water supply uncooked vegetables from soil fertilized with human excreta and flies The same author subsequently wrote that the clinical cases originating in Chicago did not lead to any considerable spread of the disease in communities to which the patients went He pointed out that control of amebic dysentery by routine examinations of stools of food handlers for the detection of carriers and their subsequent exclusion from food handling did not appear to be practicable on a large scale Nor is there he states any need

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Trichiniasis

Until drastic changes are made in the methods of garbage disposal the only effective means of control must remain with the housekeeper thi means that all pork must be thoroughly cooked before it is eaten The feeding of raw garbage to hogs is the prime factor responsible for the spread of the disea e Two recent outbreaks of trichiniasis occurred in New York City the first involving o cases among German Jewish refugees and the second 11 cases from food eaten at a church supper

Wright[8] made a study of the various methods of cooking garbage prior to feeding it to hogs as a means of preventing trichiniasis He discusses the methods used throughout the western and southern portions of the United State describ ing the equipment costs and operation The costs for fuel and labor varied from 40 cents in the South to $3 50 on the West Coast This author believes that cook ing garbage is a feasible method for the prevention of trichiniasis in hogs and thereby in human beings

In general the prevalence of trichiniasis in man is proportionate to that in hogs In Boston 28 per cent of the adults and 18 per cent of the hogs are in fected In San Francisco the rates in 1938 were 24 and 15 per cent respectively but following the institution of rodent control in the piggeries the rate of infesta tion in hogs dropped to 4 per cent in 1941 In the Hawaiian Islands 14 per cent of wild hogs were trichinous but when they were kept in concrete or wooden pens and fed cooked garbage the rate dropped to 0 3 per cent In Canada all garbage feeding hog ranches are required to be licensed and inspected and all garbage is cooked prior to feeding Inspection includes rodent control Swine trichiniasis has been reduced to 0 2 per cent

The complement fixation reaction is sensitive and specific in the serodiagnosis of trichiniasis It can be carried out as a quantitative procedure and the increase and decrease of the antibody titer can be observed over a period of time

Outbreaks of trichiniasis usually are limited to families institutions or other units that are fed from the same kitchen Four cases of trichiniasis occurred in March 194 in upper New York State A farmer who purchased a four month-old pig in the summer of 1941 rai ed it on cooked food alone In Febru ary the hog was slaughtered salted and smoked and the farmer ate the pork raw in fairly large quantities On March 3 he became ill and was hospitalized and a diagnosis of trichiniasis was made Three other members of the household be came ill with trichiniasis and a dog that had access to the meat developed ten derness of the legs Another New York outbreak resulted in 7 cases and 2 deaths in a family where a hog fed on kitchen scraps and grain was eaten Some of the meat was eaten fresh but more than half of it had been salted and cooked by

for the isolation of a case, and, when sanitary disposal of feces is practiced there is no need for special precautions in the care of stools The control of amebic dysentery, according to McCoy, depends on the diagnosis and reporting of all cases of dysentery the recognition of the etiological agent through adequate laboratory procedures the education of food handlers in personal hygiene, particularly in washing their hands after visiting the toilet, the examination of stools of food handlers during outbreaks of the disease and the provision of safe water supplies by the elimination of faulty plumbing, cross connections and similar sources of pollution

Most of the recent surveys of the prevalence of *E histolytica* indicate that Craig s initial estimate that 5 to 10 per cent of the population are infected is still correct Two to 5 per cent of first year medical and dental students in Missouri were reported positive Four per cent of 245 students at the University of Georgia School of Medicine were found positive In the post mortem examination of 202 cases of accidental death in New Orleans 13 were found to be positive for *E histolytica*

Two types of medication are effective in the treatment of amebiasis the arsenicals such as carbarsone and drugs containing iodine such as the hydroxy quinolines (chiniofon or yatren and vioform), and alkaloids, such as emetine hydrochloride

Carbarsone may be administered in capsules containing 250 mgm (gr 3 75) Usually one capsule is given twice a day for ten days for the first course and a second course of the same dosage is given a week later Chiniofon and vioform are prescribed in capsules of 0 25 gm (gr 4) three or four times a day for 7 days for the first course followed by a second after a week s interval

Emetine hydrochloride is effective in stopping the dysentery and is therefore advised early in the treatment of the disease The maximum daily dosage should not exceed 0 65 gm (gr 1) in one or two divided doses and may be given subcutaneously, intramuscularly or intravenously for four days Best results may be expected by the use of the emetine hydrochloride subcutaneously for a period of four days followed by a course of carbarsone or yatren

As a consequence of the war amebic dysentery is likely to awaken new interest in the medical profession Since it is endemic in temperate zones and is more prevalent at times even epidemic in the tropics and subtropics soldiers may become infected and bring home the disease after demobilization During World War I 926 cases of amebic dysentery were reported[1] Since our troops are more numerous in the present conflict and are in areas where the disease is prevalent, a higher incidence is to be expected

Amebiasis is discussed also in Chapt XXXIII, Vol V of Oxford Medicine to which the reader is referred for other details

[1] Vol V 344

Trichiniasis is discussed also in Chapt XXXVIII and Chapt XLI–A, Vol V of Oxford Medicine

Typhoid Fever

The gradual control of typhoid fever during the past four decades is one of the outstanding achievements of modern public health The sanitation of water supplies the control of sewage disposal the vaccination of susceptibles especially military personnel in time of war the proper handling of food and the control of known carriers have been the chief factors in its control Formerly typhoid fever was a water borne disease at present most cases are contracted from carriers who have handled food without prior washing of their hands In many instances an epidemiological investigation reveals the carrier usually a woman over forty years of age stout and perhaps with a history of gall bladder disturbances

Because the disease is becoming so infrequent (in Massachusetts the case rate dropped from 102 in 1900 to 1 2 in 1942) cases are missed sometimes by the practitioner A positive blood culture early in the disease or a positive stool culture later is often the first clue of its presence The clinical picture of protracted intestinal grip the character of the temperature rise the slow pulse the presence of rose spots constipation more frequently than diarrhea confirmation by the low blood leukocyte count the positive agglutination and the isolation of the organisms from the blood stool or urine clinch the diagnosis

The isolation of *E typhi* from stools with different types of mediums was reported by Mayfield and Gober[8] These workers made 724 isolations using three mediums as follows 535 (74 per cent) with lithium chloride endo agar 591 (82 per cent) with desoxycholate citrate agar and 601 (83 per cent) with bismuth sulfite agar They recommend that all three mediums be used routinely since not all strains were isolated with any one medium The typing of *Eberthella typhi* by the method of Craigie and Yen has assisted epidemiologists in tracing the source of outbreaks of typhoid fever If health officers adopt the typing of strains of *E typhi* usually they can ascertain the actual source of epidemics

The New Zealand Department of Health describes a milk borne outbreak of typhoid fever occurring from February to April 1942 at Otahuhu near Auckland There were 26 cases and 4 deaths and a carrier on a milk farm was responsible Removal of the carrier as a milk handler and pasteurization of the milk stopped the outbreak An unusual meat borne (souse) typhoid fever outbreak is described from Cumberland County Tennessee Seven cases resulted from souse prepared by a chronic typhoid carrier *E typhi* was isolated from the souse three months after its preparation

Three outbreaks of typhoid fever from December 1939 to March 1940

frying An upstate New York epidemic involved 19 cases and 1 death in four households The pork responsible for this epidemic was obtained from a garbage fed pig that had been made into sausages Several lots of these were given to friends thereby causing 7 cases among three other households

Spink and Augustine[7] studied 65 cases in Boston and found that in 46 per cent no relation between the disease and the food eaten was established They studied the trichiniasis infestation of rats of 193 trapped in large piggeries about twenty miles from Boston only 2 were infested of 17 captured in a meat packing house 5 (30 per cent) were infested of 70 rats caught in the Boston market or waterfront district 9 (13 per cent) were trichinous According to this study rats do not play an important role in transmitting trichinae (trichinellae) to hogs that eat them In the seven years preceding 1935 there were 7 cases among Jewish patients of the Beth Israel Hospital in Boston 4 of the patients admitted having eaten pork Diagnosis was established by biopsy and by the presence of eosino philia

In Maine an outbreak of 56 cases resulted among 71 persons who ate sausage made by an Italian from the meat of a garbage fed hog An outbreak of 64 cases occurred in a CCC camp at Waterbury, Vermont Roast pork loin, the center of which was undercooked was traced as the source The average incuba tion period was twelve days Five biopsies revealed 8 to 800 larvae per gram of muscle

About one third to one half of a company of soldiers developed trichiniasis at Camp Edwards in June 1942 after eating pork products almost daily The onset was sudden and the most frequent symptoms were malaise weakness diz ziness, frontal headaches aching of muscles of the back and extremities swelling about the eyes and gastrointestinal disturbances Persistent fever marked prostration severe headache muscle pains swollen eyelids, reddened eyes and tachycardia were prominent symptoms in the 13 soldiers that were hospitalized This outbreak emphasizes that inspection of meat does not assure safety from trichinae (trichinellae) and that the only control available to the military per sonnel is thorough cooking of all pork products

There is no specific therapy in this disease Since the worms may live for five to seven weeks in the intestine a violent purgation is recommended in order to remove those female worms which as yet have not been impregnated and which have not yet burrowed into the submucosa at the time of the treatment Three grains (0 2 gm) of calomel or an ounce of castor oil followed in four hours by a saline cathartic such as ½ to 1 ounce of magnesium sulfate are the recom mended procedures Muscle pains may be relieved by acetylsalicylic acid, hot baths and sedation Symptomatic treatment with confinement to bed may con tinue for a period of days

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The New Zealand Department of Health describes a milk borne outbreak of typhoid fever occurring from February to April 1942 at Otahuha near Auckland There were 26 cases and 4 deaths and a carrier on a milk farm was responsible Removal of the carrier as a milk handler and pasteurization of the milk stopped the outbreak An unusual meat borne (souse) typhoid fever outbreak is described from Cumberland County Tennessee Seven cases resulted from souse prepared by a chronic typhoid carrier *E typhi* was isolated from the souse three months after its preparation

Three outbreaks of typhoid fever from December 1939 to March 1940

occurred in Manitoba, Canada apparently due to cheese made from raw milk and sold without aging There were 9 cases in the first outbreak, 21 in the second and 64 in the third Investigation revealed that two workers at the cheese factory were discharging typhoid bacilli in their stools and that neither had a history of typhoid fever One of these apparently had been infected by the cheese his stools became negative in four months The other was a carrier, and typhoid bacilli were grown from his bile He had started work in November, 1939 about a month before the outbreaks began The cheese was allowed to dry for eight days and was sent to the wholesaler on the tenth day The outbreaks were stopped by removing the carrier as a milk handler and by requiring adequate aging of the cheese As a result of these outbreaks the survival of typhoid organisms in Cheddar like cheese was studied by the investigators At room temperature the organisms were detectable for one month in the refrigerator survival was prolonged In one sample *E typhi* was recovered seventeen weeks after inoculation Experiments demonstrated that the typhoid bacillus penetrates cheese by capillary traction

Bootlegged oysters were responsible for an outbreak of 81 primary and 13 secondary cases of typhoid fever in Louisiana in 1940 The outbreak was traced to a chronic carrier who gathered and subsequently infected the oysters, which were sold in the shell and opened by the purchasers

In New York a trailer camp was the focus of a typhoid fever outbreak in 1938 There were 18 cases and 3 deaths The vehicle was water from a well located in fissured limestone and subject to pollution by nearby cesspools and privies

In 1942 Massachusetts reported the occurrence of hospital infections of an intern and nurse from unrecognized cases of typhoid cholecystitis This experience recommends the protection of hospital personnel by routine antityphoid inoculation and the consideration of all patients with cholecystitis as potential typhoid carriers It is estimated that there are 1,500 typhoid carriers in Massachusetts of which only about one tenth are known to the Department of Public Health It points out that more than 3 per cent of persons who contract typhoid fever continue to harbor the organism usually in the gall bladder, during the remainder of their lives and urges physicians to make careful inquiry concerning previous typhoid fever in all cases of cholecystitis Ames and Robins[10] made a study of the age and sex factors in the development of the carrier state among typhoid fever patients in New York Patients over 30 years of age became chronic carriers nine times as frequently as did younger patients The rate of development of the carrier state at all ages was 2 per cent among males and 4 per cent among females Sixteen per cent of the female typhoid fever patients between the ages of 40 and 49 became chronic carriers By applying a modified life table based on the experience of New York these authors estimate the carrier

prevalence on January 1 1940, as 42 carriers per 100,000 population or 2 500 carriers in New York exclusive of New York City They estimate that by 1980 the carrier prevalence will decrease to about 200 Four hundred and nineteen (17 per cent) of these estimated carriers were under supervision on January 1, 1940

The treatment of this disease has undergone a great deal of change in the past years Vaccines are not efficacious in its treatment and have therefore been abandoned In 1900 the fatality rate in Massachusetts was 21 3 per cent in 1940 it was 9 3 per cent This decrease was achieved in part by the change in the concept of feeding the patient We no longer see the emaciated pot bellied convalescents The diet is mild and bland but high in calories It includes milk custards junket eggs milk toast soft cereals crackers potatoes ice cream butter and many other low residue highly nutritious foods Proper feeding next to bed rest is the most important factor in the treatment of typhoid fever Four thousand calories per day with adequate proteins to replace tissue losses and a high fluid intake are standard treatments

Early in the disease a mild saline cathartic may be administered Thereafter treatment is symptomatic Diarrhea may require the use of opiates or bismuth Hemorrhage is an indication for the use of morphine Perforation calls for immediate surgical intervention Sulfaguanidine and other derivatives of this drug may be efficacious in the treatment of typhoid the final decision as to their value must await further clinical trial

There are conflicting reports in the literature concerning the efficacy of sulfaguanidine in the treatment of typhoid carriers Levi and Willen treated favorably with 0 5 gm of sulfaguanidine per kilogram of body weight every eight hours for one week a carrier who had had a cholecystectomy prior to the use of the drug Saphir and associates treated unsatisfactorily 4 carriers with sulfaguanidine over a period of two weeks Cutting and Robson treated 6 carriers with a variety of drugs and sulfaguanidine without success One of these carriers had had a cholecystectomy prior to treatment Hoagland treated 2 intestinal carriers one chronic and one convalescent successfully by large doses of sulfaguanidine In conclusion it may be said that sulfaguanidine and succinyl sulfathiazole are equally ineffective in the treatment of typhoid carriers In our experience when treated with the former drug carriers continue to discharge the organism Kirby and Rantz likewise have demonstrated the ineffectiveness of sulfaguanidine and succinyl sulfathiazole The only sure way of curing the typhoid carrier is first to determine by bile drainage through a duodenal tube that the organisms are present in the gall bladder Then proper operative removal of the gall bladder together with the cystic duct will result in cure of the vast majority of cases

The prevention of typhoid fever is, of course, a well known story to every physician In modern large cities proper sanitation has reduced the disease to a minimum In rural communities with inadequately protected water supplies and inadequate sanitation in food handling establishments the disease is more likely to be encountered Vaccination is recommended for hospital and public health personnel vacationists and travelers Three injections, 0 5 c c, 1 0 c c 1 0 c c subcutaneously and an annual 0 5 c c are recommended, reimmunization with 0 1 c c intracutaneously is advocated by some authorities as producing less reactions and satisfactory immunity Although the United States Public Health Service recommends the use of simple monovalent typhoid vaccine, as this material produces less of a reaction and because some evidence indicates that better immunity is acquired to typhoid during wartime the U S Army and Navy both use a triple vaccine containing 1 000 million typhoid bacilli and 250 million each of paratyphoid A and B per c c[11a] as this vaccine gives a wider protection The decision as to which type of vaccine is to be used depends upon the likelihood of exposure to the various types of salmonella infection Paratyphoid A is extremely rare in the United States whereas paratyphoid B is not uncommon Vaccination is recommended for persons who are traveling or who are members of a household where there is a typhoid carrier In areas where typhoid is not prevalent, routine vaccination is not recommended as for example, in New England

Typhoid fever is discussed also in Chapt XX of Vol IV of Oxford Medicine

Paratyphoid (Salmonella) Fever

The salmonella group of bacteria formerly called the paratyphoid bacilli is composed of many species, and new ones still are being isolated Some species according to Dack[1] produce disease only in man, whereas others produce disease in animals and the infection may be transferred to man either directly by food of animal origin or through food contaminated by the excreta of rats or mice

Edwards and Bruner[13] at the Kentucky Agricultural Experiment Station in Lexington Kentucky typed 3 090 cultures of salmonella from 2,285 outbreaks in man and animals from thirty six states *Fifty nine types* were encountered of the cultures isolated from man 99 per cent were members of groups A B, C, D and E of the Kauffmann White schema The frequency of the occurrence of the various types in man and animals is strikingly similar Some of the species are confined largely to man and others largely to animals, but the great majority are found in a number of animal species and in man a fact that emphasizes the lack of host specificity of most salmonella types The possibility of direct transference of salmonella infection from animal to man is obvious On the other

hand the isolation of bacilli of this type from such a large number of normal human carriers indicates how often outbreaks of salmonella organisms may originate from food handlers who are carriers of these bacilli

Welch and associates [4] conducted laboratory experiments on the role of rat in the spread of salmonella infections The excreta of rats that were naturally infected with *S enteritidis* when held at room temperature contained living organisms for at least 148 days Cross infection between mice and rats took place in cages These authors examined 4 0 specimens of murine excreta 80 mouse and 340 rat collected from all parts of the country and found only 1 per cent positive for salmonella Certain rat exterminators known as rat virus contain salmonella organisms This is a dangerous procedure since the salmonella is pathogenic for man Spray reported an outbreak in 1926 involving 135 cases traced to milk presumably contaminated with rat virus

Ostrolenk and Welch[t] experimented with the house fly *Musca domestica* as a vector of *S enteritidis* Flies fed on food infected with this organism are capable of infecting other flies as well as food water and miscellaneous surfaces with which they come in contact The organism apparently survives in the fly for the duration of its life about four weeks These authors observed the transfer of *S enteritidis* from flies to mice and their retransfer from mice to flies Moreover fly eggs planted in mash and infected with *S enteritidis* resulted in infected maggots pupas and adults In view of all these experiments foods should be protected from both rats and flies since these may act as vectors of salmonella

Rubin and associates reported the finding of 13 types of salmonella in the mesenteric lymph nodes of apparently normal hogs in Lexington Kentucky Of 40 lots containing 25 animals each 19 47 per cent gave positive culture Fifty hogs were examined individually 5 10 per cent yielded salmonella Cherry and associates cultured 250 samples of meat from 58 retail markets in Lexington Of 170 samples of pork and 2 mixtures of beef and pork 6 2 per cent yielded salmonella 2 5 per cent of 64 samples of beef yielded salmonella whereas 11 samples of lamb gave negative results Eight types of salmonella were isolated These authors were convinced that the animals themselves were the source of the salmonella since there was no correlation between the sanitation of the retail markets and freedom from organisms

The classification of the salmonella paratyphoid group was initiated by White and was extended further by Kauffmann In 1934 a subcommittee of the International Society for Microbiology standardized the terminology Before the outbreak of the present war an international salmonella center was established under the auspices of the Commonwealth Fund at Copenhagen by Dr Thorvald Madsen A detailed description of salmonella typing

can be found in the second edition of Bacteriology and Immunity by Topley and Wilson[18]

Savage[19] in a study of salmonella infections concluded that the presence of the organisms in a stool of a patient means an active infection or the carrier state The different types of salmonella, he states, are serologically distinct, produce no considerable amount of cross immunity and cause characteristic pathological manifestations Three types of clinical pictures predominate, continued fever (enteric) acute gastroenteritis (food poisoning) and general infection (septicemic) Salmonella bacilli cause disease in man, animals and birds, one must therefore, look to salmonella animal diseases for sources of food poisoning *S paratyphi A* *S paratyphi B* and *S schottmuelleri* produce an enteric type of disease *S aertrycke* and *S enteritidis* cause gastroenteritis, the latter occasionally producing a septicemia *S enteritidis* may produce any of the three types, *S suipestifer* causes gastroenteritis or septicemia

Hinden[20] describes an outbreak due to *S aertrycke* among children of an English hospital ward Of 14 in the ward only 3 bottle fed babies escaped 11 children 2 attending physicians and 11 nurses were ill with diarrhea The author states that there were 299 outbreaks of salmonella food poisoning affecting 4,418 persons with 102 deaths between 1923 and 1937 in England an annual average of 20 outbreaks *S aertrycke* was responsible for 169 of these

Savage[19] made an epidemiological study of paratyphoid fever in Great Britain There were 40 outbreaks from 1923 to 1941 inclusive with a mortality of 1 76 per cent The incubation period averaged 7 to 24 days Ice cream was the vehicle responsible for most cases among children Sixty per cent of the outbreaks started in May June or July Cream was the vehicle in 40 per cent , and food was responsible for 80 per cent Water borne paratyphoid fever was comparatively rare Savage brings out two most important epidemiological factors if the vehicle containing the bacteria was kept for long periods in warm weather, the attack rate was high and the source of most of the outbreaks was an ambulant unrecognized or subclinical case

An outbreak due to *S aertrycke* from duck eggs involved 55 boys and 16 adults in an orphanage in this country The eggs were used in the preparation of rice pudding The same organism was isolated from the feces of 9 ducks and from the oviducts of 2 the blood of 3 ducks gave positive agglutination tests Seven British outbreaks are described in which duck eggs were the vehicle of infection The largest outbreak in this series involved more than 300 persons with 1 death, the food being ice cream made with duck eggs *S aertrycke* was responsible for these outbreaks this organism can penetrate the shells of duck and hen eggs when applied and kept moist

S typhi murium was isolated from a turkey and turkey dressing served in a

mental institution there were 238 cases and 1 death The manner of infection of the turkey was not ascertained One patient continued to carry the organism for 18 weeks Smoked whitefish was responsible for an outbreak of 34 ca es and 1 death in New York City in 1934 a second outbreak in July 1940 resulted in 47 cases and deaths in New York City and 1, cases in upstate New York Smoked fish carp, whitefish and butterfish were purcha ed from 12 different Brooklyn neighborhood delicatessens and were traced through a wholesaler to a smokehouse in upstate New York Samples of ditch water the drainage from the washing soaking and salting vats contained *S typhimurium* The same organism was isolated from 14 customers (patients) 3 food handlers (patients) 1 whole saler (a patient) 1 of the processors who was not ill and 5 samples of the smoked fish

The treatment of paratyphoid infections is similar to that of typhoid fever In many instances however the disease is milder of shorter duration and the patients are ambulatory Often asymptomatic infections occur

In general vaccination against paratyphoid infections is not recommended except in specific instances since this disease is caused by a large number of dif ferent organi ms with very little cross immunity Vaccination is recommended for military personnel for travelers to foreign countries where paratyphoid A is more prevalent and for employees of hospitals and institutions where paratyphoid B outbreaks are not uncommon A combined triple vaccine, such as is manu factured by the U S Army can be used for simultaneous protection against typhoid and paratyphoid A and B (see section on Typhoid)

In discussing the treatment of clinical dy entery with sulfathiazole in chil dren Rubens Kaplan Borovsky and Blatt [1] bring out three interesting facts Their series of cases at the Cook County Hospital Chicago consisted of 9 children with negative and 8 children with positive stool cultures of shigella and salmonella who were treated with sulfathiazole A control series of 16 children with negative and 13 with positive stools were not given the drug Patients with clinical dy en tery and with positive stool cultures responded to sulfathiazole better than did the group with clinical dysentery and negative stool cultures The duration of disease after sulfathiazole treatment was 2 9 days in the treated patients com pared with 4 7 in patients not receiving sulfathiazole Patients with clinical dysentery and positive stool cultures who were treated with sulfathiazole had diarrhea of shorter duration than did those not so treated the durations in the treated and untreated cases being 2 9 and 8 8 days respectively These authors administered 0 1 gm (gr 1½) of sulfathiazole per pound of body weight per day in six equal doses every four hours

Paratyphoid fever is discussed also in Chapter XXI Vol IV of Oxford Medi cine

Bacillary Dysentery

Bacillary dysentery is a serious problem, especially in small villages and rural areas where it is more prevalent than it is in urban areas The ordinary sanitation methods that resulted in the lowering of typhoid fever rates have not been effective in lowering the incidence of bacillary dysentery Annually many localized epidemics occur especially in summer resorts and institutions Two types, Flexner and Sonne bacilli are of about equal importance in the United States Proper sanitation of milk water and food supplies must be instituted to control this disease Bacillary dysentery may be considered to be even more serious than typhoid fever since it is more prevalent and disabling and has a higher mortality The usual methods of dissemination are unrecognized cases, mild or severe clinical cases and temporary or chronic carriers The disease is extremely prevalent in China Of 315 cases in Chinese children from birth to eleven years of age the causative organism was isolated in 67 per cent of the cases This high prevalence of bacillary dysentery in countries with primitive sanitation is to be expected The reported incidence for 1938 in the Philippines was 40,503 cases and 16 034 deaths from typhoid fever dysentery and diarrhea or enteritis Of these deaths 12,158 76 per cent were caused by diarrhea or enteritis alone The peak of morbidity and mortality was in June July and August The incidence and mortality were highest in the age group from birth to four years Primitive sanitation especially open latrines are responsible for this high incidence In Manila food is the main vehicle for the spread of these diseases

Watt Hardy and DeCapito state that convalescent and passive carriers of dysentery bacilli occur commonly In 103 positive cases 82 patients 80 per cent were convalescent carriers described as harboring the organisms after clinical recovery The average duration of illness was 11 days The average minimum duration of infection was 27 days and known convalescent carriers continued positive for an average of 34 days These authors found that the average illness due to Flexner infection was more prolonged than that due to Sonne or Newcastle They conducted 6 324 survey stool examinations in New Mexico Georgia and Puerto Rico 239 patients 3 8 per cent were carriers of dysentery bacilli This high incidence is in contrast to New York City where of 1 659 stools examined only 2 0 1 per cent were positive This difference in carrier rates is in direct proportion to the incidence of the disease in these areas and to the advancement of environmental sanitation

In 1933 there were 625 reported cases of bacillary dysentery and 17 042 cases of unclassified diarrhea in New York In 1940 there were 19 152 cases of bacillary dysentery and only 1 484 of unclassified diarrhea New types of strains of dysentery bacilli are being recognized seven were discovered between 1933 and

1940 For example in 1940 the Newcastle bacillus which formerly had been found only in Africa England India and South America was isolated from three different areas in the United States New Mexico Georgia and New York City

Macumber [3] studied 263 consecutive cases of bacillary dysentery treated from 1930 to 1941 at the Gorgas Hospital Panama Canal Zone During this time all the cases were sporadic except for one major outbreak of 33 cases of Flexner type in an army post This author observed a ca e fatality of 6 5 per cent The u e of polyvalent serum failed to reveal evidence that such therapy was of value Flexner organisms were isolated from 91 per cent of the cases and Sonne organ i ms from 6 5 per cent no Shiga bacilli were obtained The stools of 2 206 food handlers were examined and only 5 were found to harbor Shigella organisms 2 contained Flexner and 3 Sonne bacilli

A considerable advance has been made in the laboratory diagnosis of this disease The comparative efficiency of differential mediums has been studied by many Desoxycholate citrate medium isolates a much higher percentage of shigella organisms than do plain endo lithium chloride endo and bismuth sulfite agars A comparison of the desoxycholate citrate and difco s s (shigella sal monella) agar revealed that the latter is even more efficient

Numerous sporadic outbreaks of bacillary dysentery occur annually and many find their way into the literature It is not unlikely that this group of diseases is causing disability among the armed forces as they enter areas with primitive sanitation where the disease is relatively prevalent

The predilection of shigella infections for institutions and summer resorts is illustrated by the following outbreaks The first an institutional one in Connecticut was traced to ice contaminated by a woman handler who herself was ill with the disease Ninety per cent of the physicians nurses and waitresses were ill with Flexner dysentery The ice was added to pitchers of drinking water in the doctors and nurses dining rooms An outbreak of Flexner dysentery in New York caused 105 cases among 340 boys in a summer camp The vehicle was raw milk infected by one or more milk handlers Two milk borne epidemics were traced to a single dairy in a small village in rural New York The first outbreak consisted of 134 cases of Flexner dysentery Five months later 73 cases of scarlet fever with 3 deaths were traced to the same dairy After these two outbreaks the village finally passed an ordinance requiring the pasteurization of milk In another institutional outbreak there were 97 cases of bacillary dysentery due to the Newcastle bacillus chiefly among nurses in a hospital in New York City The organism was isolated from 76 of 97 cases The vehicle was food prepared in the kitchen of the nurses home where it was contaminated by an undetected carrier A hospital epidemiologist especially trained preferably at the expense of the hospital is highly effective in the control of bacillary dysentery An

outbreak of Flexner dysentery associated with infectious jaundice was investigated in a state school in Vermont There were 32 cases with dysentery alone 26 with dysentery and jaundice and 62 with jaundice only The jaundice occurred about one week after the dysentery The outbreak was traced to a carrier in the kitchen as the probable source Unclean clothing may also have been a factor in its spread Flexner bacilli were isolated from 5 patients with dysentery only from 2 with both dysentery and jaundice and from 5 with jaundice only

The possibility of war prisoners as foci of outbreaks is cited by two British sources The first reports the isolation of shigella from 4 Italian prisoners who had had no symptoms for 3 to 15 months previously The Emergency Public Health Laboratory Service reported culturing 900 stools from 300 Italian prisoners Some specimens were plated directly on MacConkey agar, whereas other were inoculated into tetrathionate broth and plated after eighteen hours Fifty one prisoners were found to be infected with dysentery bacilli The transportation of large numbers of men is a means of spreading a variety of diseases into areas where the disease does not exist Apparently the British authorities are exercising precautions to limit the transportation of disease to a minimum

The therapy of bacillary dysentery has undergone a great change in the past few years In China the cases at Peiping were treated with regulation of diet and increased fluid intake Drug therapy did not seem important This view however is at variance with that of most authors In 1939 Lawrence [4] reported in vitro studies in which sulfathiazole was found to be the most effective of the sulfonamide drugs then available against the colon typhoid dysentery group of organisms Below sulfathiazole in effectiveness were sulfapyridine sulfamethyl thiazole and sulfanilamide in that order Cooper and Keller comparing the effectiveness of sulfathiazole sulfapyridine sulfamethylthiazole and sulfanilamide in protecting mice against fatal doses of *Shigella paradysenteriae* (Flexner) found sulfathiazole to be the most effective and sulfanilamide the least effective Libby s [6] work revealed that in vitro sulfathiazole is more effective against the Flexner bacillus than are the other sulfanilamide compounds Good results in the sulfathiazole treatment of infectious diarrhea have been reported by many workers Some of these studies, however were inadequately controlled Cooper and his associates report that sulfathiazole is of greater therapeutic value in patients whose stools are positive for dysentery organisms than in those whose stools are negative for these pathogens

Hawking [5] in 1942 studied the concentrations of various sulfonamides in the feces of cats mice and men In cats the highest concentration of all compounds was observed In mice sulfathiazole seemed more effective than sulfaguanidine in diminishing the number of bacteria but the dosage required was toxic In men sulfaguanidine was found in the feces in high concentrations but sulfapyri

dine, sulfathiazole sulfadiazine and sulfanilylbenzamide were found in fairly low concentrations These experiments indicate that sulfaguanidine is the drug of choice for the treatment of bacillary dysentery

Most authors write favorably of sulfaguanidine as shortening the clinical course of the disease reducing the number of stools per day and helping to prevent the convalescent carrier stage Lyons of the United States Navy treated 23 cases with sulfaguanidine and had 23 cases as controls Five cases were not aided by the drug 18 however had striking benefits There was a fall in temperature and leukocyte count in 24 to 48 hours with concomitant reduction in the number of stools and clinical improvement The drug was administered as a powder in milk 0 1 gm (gr 1½) per kilogram of body weight as the initial dose followed by 0 05 gm per kilogram (gr ¾) every 4 hours until the number of stools was less than 5 per 24 hours Thereafter the dosage was reduced to 0 05 gm (gr ¾) per kilogram every 8 hours for the next 48 to 72 hours

Anderson Cruickshank and Walker used sulfaguanidine in 41 adults who had Flexner dysentery with beneficial results as compared with 55 controls The dosage was 9 gm (gr 135) per day in 3 gm (gr 45) doses for 2 days followed by 4 gm (gr 60) per day in 2 gm (gr 30) doses If the diarrhea was not controlled in 4 days a maintenance dose of 4 gm (gr 60) per day was continued for a week Such high dosages were beneficial and without toxic effects Patients however must have a high fluid intake to prevent crystallization of the drug in the urine Sulfaguanidine therapy is indicated for both cases and carriers Best results are obtained in treating the Flexner and Newcastle varieties where patients cease to have shigella in the stools by the tenth day as compared with untreated cases where the organisms were isolated for two to three months The conclusion concerning the efficacy of the drug in the Sonne variety of dysentery is guarded since these cases required a greater dosage over a longer period of time and do not become negative as quickly as do those with the Flexner and Newcastle varieties Succinylsulfathiazol has proved to be effective in the treatment of 5 dysentery carriers as demonstrated by Kirby and Rantz These authors however fail to identify the dysentery organisms as found in these patients This drug is about equal to sulfaguanidine in the treatment of these carriers and has less toxic effects since less of it is absorbed into the blood stream

Fairley and Boyd[1] treated 371 cases of bacillary dysentery 135 of which were caused by the Shiga bacillus in the Middle East In the 96 cases with complete records that were analyzed the earlier the treatment with sulfaguanidine the less damage was there to the colon and the quicker was the recovery This chemotherapy was also effective against the Flexner Schmitz and Sonne varieties but no data are given These authors report favorably on the use of specific antitoxin for the treatment of patients infected with the Shiga variety of dysentery

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Three types are recognized pernicious, undulant and continuous A positive agglutination test at a titer of 1 80 or higher is significant however it must be remembered that agglutinins may persist in the blood for 4 to 10 years A skin test with 0 05 c c of a killed suspension of organisms injected intracutaneously or a 1 10 000 dilution of Huddleson s brucellergin gives induration as a positive response Its interpretation however must be guarded

There are four modes of infection the ingestion of raw milk or raw milk products the handling of infected animal discharges or the carcasses of infected animals the consumption of inadequately cooked meat of an infected animal and contact with brucellosis patients The first mode is by far the most frequent the last two are rare Reinfection may be a factor in chronic brucellosis since the disease is unrecognized and the patient continues to consume the brucella laden raw milk

In diagnosis the clinical picture is the most important factor laboratory procedures are secondary The most reliable procedure is the culture of the organism The second most reliable aid is a high titer of agglutinins in the serum It is well to remember that 6 to 10 per cent of culturally positive cases fail to develop agglutinins The agglutination test therefore should not be used diagnostically to eliminate brucellosis The intradermal or skin test is the third most useful one It is performed with a killed suspension of organisms a filtrate or a protein derivative A positive skin test however does not necessarily indicate that the active disease is brucellosis it means only that the patient has had contact with brucella either past or present The skin test does not distinguish between past or present or latent and active disease The patient may never have been a clinical case of brucellosis An opsonocytophagic index may give aberrant results in some cases Fluctuations occur rapidly in convalescent and recovered patients over short periods of time

The prevalence of contagious abortion of cattle and undulant fever in man was reduced in Saskatchewan by requiring in certain districts the annual testing of dairy herds before milk was sold and by the education of stock owners in the desirability of having healthy disease free cattle The 1933–1939 data gave 5 68 per cent of cows and 4 34 per cent of men as infected in 1938–39 only 4 34 per cent of cows and 2 11 per cent of men were infected In Massachusetts the situation apparently is reversed There has been a gradual increase in the number of reported cases This increase however is more apparent than real and is explained in part by greater interest in this disease and in part by better diagnostic laboratory aids The number of cases in Massachusetts more than doubled from 1931–1935 when 98 were reported to 1936–1940 when there were 27 Of 325 cases 85 were in communities of over 25 000 population and 240 in communities of less than 25 000 Moreover some of the patients in the larger com

bacillus Human convalescent serum has been tried in the treatment of bacillary dysentery, but this therapy must receive further evaluation Clinical and experimental observations indicate the possible existence of acquired immunity, and active and passive immunization with vaccine and human convalescent serum likewise have been tried experimentally but as yet are not generally accepted

Much research has been carried out on the possible toxic manifestation of Shigella infections Some authors believe that definite constitutional symptoms are produced by the action of soluble toxins circulating in the blood However, no one has yet successfully applied this theory to the therapy of human dysentery As a matter of fact experience indicates that a polyvalent dysentery serum is not efficient as a therapeutic agent Shiga antitoxin seems to be the only preparation that has proved of clinical value Sulfaguanidine remains the therapy of choice

Bacillary dysentery is discussed also in Chapt XXIII, Vol IV of Oxford Medicine

Brucellosis

Undulant fever which once was responsible for an epidemic of unknown fever among British soldiers on the island of Malta was imported to the United States in 1905 with a shipment of goats from Malta In 1911 it was recognized as endemic in Texas Three varieties of Brucella are recognized *Br melitensis* a caprine strain *Br abortus* a bovine strain and *Br suis* a porcine strain Although these organisms can penetrate the unbroken skin, most infections are acquired through the digestive tract The vehicle in most cases is raw milk The disease has been recognized in Canada since 1929

Huddleson s Brucellosis in Man and Animals is a recognized work containing details on the epidemiology pathology clinical types, analysis of symptoms and treatment of this disease He reviews 21 cases Harris[33] devotes a major portion of his text to the symptomatology and diagnosis of clinical and subclinical infections The prevalence according to him is wide Eleven to 20 per cent of the cows in the United States are infected and 20 per cent of the hogs in Iowa are victims of brucellosis

The importance of brucellosis of cattle Bang s disease or infectious abortion, was studied by Eichhorn and Crawford[34] of the United States Department of Agriculture They evaluate the various methods of controlling the disease in animals such as the vaccination of cattle the testing and slaughter of positive reactors herd management the testing and segregation of reactors and the prevention by proper examination of new additions to herds

Brucellosis appears to be on the increase in the population of the United States All ages and both sexes are susceptible the average incubation being 14 days

Three types are recognized pernicious undulant and continuous A positive agglutination test at a titer of 1 80 or higher is significant however it must be remembered that agglutinins may persist in the blood for 4 to 10 years A skin test with 0 05 c c of a killed suspension of organisms injected intracutaneously or a 1 10,000 dilution of Huddleson s brucellergin gives induration as a positive response Its interpretation however must be guarded

There are four modes of infection the ingestion of raw milk or raw milk products the handling of infected animal discharges or the carcasses of infected animals the consumption of inadequately cooked meat of an infected animal and contact with brucellosis patients The first mode is by far the most frequent the last two are rare Reinfection may be a factor in chronic brucellosis since the disease is unrecognized and the patient continues to consume the brucella laden raw milk

In diagnosis the clinical picture is the most important factor laboratory procedures are secondary The most reliable procedure is the culture of the organism The second most reliable aid is a high titer of agglutinins in the serum It is well to remember that 6 to 10 per cent of culturally positive cases fail to develop agglutinins The agglutination test therefore should not be used diagnostically to eliminate brucellosis The intradermal or skin test is the third most useful one It is performed with a killed suspension of organisms a filtrate or a protein derivative A positive skin test however does not necessarily indicate that the active disease is brucellosis it means only that the patient has had contact with brucella either past or present The skin test does not distinguish between past or present or latent and active disease The patient may never have been a clinical case of brucellosis An opsonocytophagic index may give aberrant results in some cases Fluctuations occur rapidly in convalescent and recovered patients over short periods of time

The prevalence of contagious abortion of cattle and undulant fever in man was reduced in Saskatchewan by requiring in certain districts the annual testing of dairy herds before milk was sold and by the education of stock owners in the desirability of having healthy disease free cattle The 1933–1939 data gave 5 68 per cent of cows and 4 34 per cent of men as infected in 1938–39 only 4 34 per cent of cows and 2 11 per cent of men were infected In Massachusetts the situation apparently is reversed There has been a gradual increase in the number of reported cases This increase however is more apparent than real and is explained in part by greater interest in this disease and in part by better diagnostic laboratory aids The number of cases in Massachusetts more than doubled from 1931 1935 when 98 were reported to 1936–1940 when there were 2 7 Of 325 cases 85 were in communities of over 25 000 population and 240 in communities of less than 25 000 Moreover some of the patients in the larger com

munities probably were infected while on vacation or during visits to smaller communities where they consumed raw milk The symptoms in order of frequency were fever, chills, sweats, weakness, headache and general aches Of 337 patients 212 64 per cent used only raw milk, 52, 15 4 per cent, both raw and pasteurized milk and 32 9 per cent pasteurized milk

The increase of undulant fever in Massachusetts occurred in spite of the fact that 90 per cent of the population in 1940 were using pasteurized milk Two outbreaks of undulant fever with 7 and 5 cases respectively occurred between 1933 and 1940 In 1941 *Br suis* was isolated from a raw milk supply in a central Massachusetts town This supply was responsible for 14 recognized cases of brucellosis the largest single outbreak on record in Massachusetts

An extensive outbreak of undulant fever due to *Br suis* occurred in Iowa in 1941 Seventy seven cases were diagnosed as brucellosis on the basis of positive clinical or agglutination findings *Br suis* was isolated from the raw milk supply

Br melitensis likewise has been isolated from cow s milk Duke reports finding this variety in the milk from 3 of 76 cows in a herd that had been accredited for 14 years on a farm where goats had never been kept An epidemic due to *Br melitensis* was reported among students who took courses in a laboratory building at Michigan State College There were 45 clinical and 49 subclinical cases The manner in which the students became infected was not ascertained

Menton[36] isolated *Br abortus* from 29 per cent of milk samples from cattle whose serums contained agglutinins and from 9 per cent of those that did not This work illustrates the fact that the same phenomenon occurs in cattle as in human patients namely a certain percentage 9 per cent in cattle and 6 to 10 per cent in men do not develop agglutinins in spite of the cultural demonstration of infection with brucella

Wise and Poston [7] cultured 14 consecutive cases of Hodgkin s disease and isolated brucella in all When 67 patients from the same area with lymphosarcoma leukemia or tuberculous adenitis were cultured no positive results were obtained with one exception There seemed to be some correlation between the brucella infection and the clinical course However, many more data are necessary before one can assume that the brucella organisms are the etiological agents of the clinical manifestations of Hodgkin s disease

The evaluation of therapeutic agents still is pending Since the disease is greatly varied and is prone to improve or lapse spontaneously, more extensive and more accurate control data than those currently available are necessary before definite conclusions can be reached Simpson does not encourage the use of sulfanilamide Huddleson[4] and Harris[33] both advocate the use of vaccine or brucellergin for the treatment of chronic and selected cases Harris believes that chemotherapy with sulfonamides may prove beneficial Sarvis[35] treated 3 cases

with sulfaguanidine with apparent cure Caution however must be exercised in the evaluation of therapeutic procedures because of the protean nature of the disease and because of its tendencies to spontaneous remission or relapse Certainly much further experimentation under properly controlled conditions is required before a final opinion on the efficacy of specific therapy or chemotherapy can be given

Brucellosis is discussed also under the title Undulant Fever in Chapt XXV, Vol IV of Oxford Medicine

Streptococcal Infections

The usual vehicle for food borne hemolytic streptococci is raw milk In upstate New York from 1917 to 1941 there were 168 milk borne outbreaks with 9 989 cases 57 34 per cent of the outbreaks which involved 6 812 68 per cent of the cases were due to streptococci causing septic sore throat and scarlet fever All of them were due to raw milk except one where improperly pasteurized milk was incriminated From 1935 to 1942 there were 9 outbreaks in upstate New York due to hemolytic streptococci One of these with 44 cases of scarlet fever due to a type 3 group A streptococcus was traced to an infected cow s udder The raw milk was secured at a local cheese factory where the milk of 6 069 cows was pooled The cow responsible for the outbreak was located by a Breed smear and a bacteriological follow up of the suspected herds The cow had suffered a teat injury that was later infected through manipulation by a person with a sore throat

In April 1942 6 cases of scarlet fever and 24 of septic sore throat were traced to raw milk coming from a cheddar cheese plant in a small community in Delaware County New York Epidemiological evidence suggests that the ultimate source of contamination was one of the numerous producers who brought to the plant 150 000 pounds of milk daily

In Massachusetts from 1933 to 1940 there were 6 milk borne outbreaks with 400 cases 4 consisted of scarlet fever or sore throat and were responsible for 412 cases

In July 1941 a ham borne streptococcal outbreak occurred in a small town in Massachusetts One of two hams was infected by a woman who was in the pre eruptive stage of scarlet fever The hams were ground and the meat made into sandwiches which were left standing at room temperature for 24 hours on a hot summer day and then served to 200 people As a result there were 4 cases of scarlet fever 50 cases of septic sore throat 7 of diarrhea 7 of nausea and vomiting and 8 of miscellaneous complaints Gastrointestinal symptoms were unusually prominent in all the patients A hemolytic streptococcus type 2 group

A was isolated from the throat of the responsible food handler, from the ground ham and from the throats of several patients Animal experimentation and other laboratory procedures suggest that an enterotoxic substance not dissimilar to staphylococcal enterotoxin may have been responsible for the unusually large incidence of nausea, vomiting and diarrhea

An outbreak of streptococcal septic sore throat and scarlet fever transmitted by food other than milk was reported in a western United States Army camp There were 341 cases in one of the units About one fourth of these patients developed a typical scarlet fever rash The streptococcus was type 15, group A There were no fatalities and complications such as peritonsillar abscess and otitis media were uncommon

The treatment of food borne streptococcal infections is the same as that of similar diseases acquired through other means Chemotherapy, using the sulfa drugs is indicated only in complicated cases The gastrointestinal symptoms usually are of short duration and after the initial vomiting and purging do not require treatment unless protracted Fluids should be given in generous amounts

Streptococcal infections are discussed also elsewhere in Oxford Medicine see Chapt XXVIII–A Hemolytic Streptococcus Pneumonia Chapt XXIX Erysipelas, Chapt XXX Septicemia in Vol IV and Chapt I, Septic Sore Throat Chapt II Rheumatic Fever Chapt XXI Scarlet Fever in Vol V

Food Poisoning

Botulism

Botulism is due to the production of a heat labile toxin formed by the germinating spores of *Clostridium botulinum* in underprocessed canned foods Two varieties types A and B, are encountered usually in the United States recently cases due to type E were reported in California To quote Dack[1] "War conditions in 1917–18 served as a stimulus to preserve more food, and at that time the danger of botulism was not recognized Hence considerable spoilage from under processing was encountered with an occasional outbreak of botulism Research to determine the cause of spoilage showed that the cold pack method of processing foods for home canning as recommended by the government at that time was entirely inadequate to prevent botulism "

During the ten years from 1931 to 1940 inclusive, there have been an average of 11 outbreaks each year From 1899 to 1941 according to K F Meyer, there were 357 outbreaks in the United States and 2 in Canada In Great Britain only 2 outbreaks have been recorded Prior to 1922 62 per cent of the outbreaks in California were due to home canned apricots, pears, string beans, asparagus and

corn and commercially packed ripe olives and spinach Only 24 per cent were due to animal products which are the usual source of botulism in Europe Dack analyzed the foods responsible for 357 outbreaks between 1899 and 1941 The foods most frequently involved were string beans (80 outbreaks 3 with commercial canning) corn (36 1 with commercial canning) spinach or chard (21 10 with commercial canning) beets (16 2 with commercial canning) asparagus (13 none with commercial canning) olives (13 12 with commercial canning) beans (10 none with commercial canning) The amount of acidity in the food is an important factor in determining the limits of growth of *Cl botulinum* Growth is uncertain at pH 5 4 or lower The food may or may not give evidence of spoilage such as a foul odor or a sharp taste

Prior to 1935 botulism was unknown in South Dakota and *Cl botulinum* could not be isolated from the soil In that year however the disease made its appearance as an epidemic of limber neck among chickens fed on home canned corn that showed signs of spoilage The following year a family outbreak occurred String beans that had been home canned by the cold pack method were slightly foamy and faintly rancid They were rinsed in cold water and served to 5 persons Four ate them and died within 42 hours 1 did not and kept well Many chickens ranging in the back yard died of limber neck presumably after drinking from a puddle into which the kitchen sink drained Type A *Cl botulinum* was isolated from the beans The investigators conclude that canning by the cold pack method should be discontinued if further outbreaks of botulism are to be avoided

A family outbreak of botulism in California involved 3 cases with 1 death The family of 6 ate for supper macaroni prepared with commercially canned mushroom sauce designated as Italian style milk apples and oranges The sauce was not heated but was poured directly over the cooked macaroni before serving The 3 children who were affected obtained the first servings Three other members of the family ate the same meal but did not become sick The incubation periods in the 3 sick children were 10 17 and 20 hours respectively The can was not a swell (a can bulged by fermentation) and the sauce was normal in appearance and taste It had been manufactured in California from mushrooms that had been dried in Yugoslavia and shipped in sealed cans In manufacture the cans (No 1 size) had been heated at 245 F for 45 minutes The pH of other cans varied from 4 2 to 4 9 Type E *Cl botulinum* was obtained from the sides of the empty tin

The New York State Department of Public Health calls to the attention of health officers the possibility of an increase in cases of botulism from home canned foods because of the larger numbers of Victory gardens and the subsequent home canning of foods Between 1922 and 1941 there were 36 cases with 14

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after boiling for 30 minutes, and chlorine in palatable amounts is not effective in destroying it

The laboratory procedures and the characteristics of the enterotoxin are described by numerous authors and are especially well reviewed by Dolman[4]. Not all staphylococci give rise to food poisoning. However, if *Staph aureus* is found in abundance in a suspected food, this is presumptive evidence that it is the offending agent. Final proof of whether the isolated strain is a food poisoning type rests on animal experimentation.

It is often found desirable to classify a strain of staphylococcus in order to obtain positive evidence in an outbreak. If specimens that are isolated from the food, from the food handler and from the vomitus of patients are identical, this is the best proof of the sequence of the outbreak.

There are various methods whereby food may be infected with staphylococci. An outbreak was traced to commercially prepared egg and olive sandwiches contaminated by a carrier. Another one was due to buttermilk. An elderly woman infected a can of soup from a whitlow of the left thumb. The soup was left standing at room temperature for 7 days, then heated and eaten. Three hours later the woman became ill with vomiting and diarrhea and died on the same day. A strongly hemolytic, coagulose positive strain of *Staph aureus* was isolated from the empty can and from the stomach and intestinal contents. In Worcester, Massachusetts, a woman prepared soup from a dehydrated mix and left it standing for 28 hours; it was then heated and eaten by the woman and her granddaughter. Both were ill with severe nausea, vomiting and diarrhea 3 hours later. *Staph aureus* was isolated from the left over soup. Two other packages of the same lot of dehydrated soup were free of staphylococci.

Coughlin and Johnson[13] reviewed 17 staphylococcal outbreaks with 1 227 cases between 1935 and 1939 in upstate New York. All were traced to cream filled pastry. Five of the outbreaks, responsible for 60 per cent of the cases, were from a single bakery. Chocolate eclairs and cream puffs were involved most commonly, and contrary to popular belief the outbreaks occurred in the colder months as well as during the summer. The authors recommended the rebaking of filled pastry and prompt sale as methods of control. New York State reported the following recent food poisonings due to staphylococci. Twenty eight patrons of a first class restaurant in an upstate city became ill with profuse vomiting, diarrhea and marked prostration 5 hours after a meal. The vehicle was hollandaise sauce, which is made from butter, egg yolks, lemon juice, water and salt. Sixteen persons in New York City were served a dinner at a hotel in March 1942. From 3 to 8 hours later all but one became ill with diarrhea, cramps, nausea and vomiting, which lasted for 2 to 3 days. The only person who was not ill had not eaten hollandaise sauce. The sauce had been prepared

deaths in upstate New York The department urges consumers of home canned foods to boil them for at least 15 minutes after removal from the containers Data collected from the health departments of the New England states revealed that botulism is rare in this region From 1920 to 1942 there were no known cases or deaths due to botulism in any of the states except Connecticut which reported 5 cases, 2 in 1922, and 1 each in 1925, 1933 and 1942

In Oregon Watson[39] treated 16 cases of botulism with a case fatality rate of 30 per cent He states that large doses of bivalent (types A and B) antitoxin are imperative in the treatment of the disease Prompt intravenous administration followed by repeated intramuscular injections was described as the most satisfactory procedure Oxygen administration is recommended by this author who used the respirator when respiratory paralysis seemed imminent Most writers, however consider the specific treatment of the disease unsatisfactory The mortality rate is usually 60 to 70 per cent

The United States Department of Agriculture bulletin entitled 'Home Canning of Fruits Vegetables and Meats '[40] contains detailed instructions not only for the correct handling and processing of foods but also for their safeguarding against spoilage from *Cl botulinum* and other dangerous bacteria

Botulism can be prevented if home canning is properly performed Special care must be taken in the immediate future because underprocessing of home canned products may occur frequently now that home canning is stimulated by the rationing of commercially canned foods Proper precautions must be taken by all canners especially by those who are canning for the first time The fruits and vegetables should be fresh and firm and should be thoroughly washed, cleaned and canned as soon as possible after harvesting Non acid food such as vegetables meat poultry and fish should be processed in a pressure cooker according to Faust[41] of the United States Department of Agriculture If a cold pack method is employed in home canning the food should be reboiled for 10 to 15 minutes before tasting or eating Canned food that is foul in odor has an off or sharp taste or gives off gas on being opened should be discarded preferably without tasting since the toxin is extremely powerful and may cause severe illness even in minute doses

Botulism is discussed also in Chapt XI Vol V of Oxford Medicine

Staphylococcal Poisoning

Dack[11] states ' staphylococcus food poisoning like botulism, is produced by a toxin formed in the food before ingestion It is probably the most common of all food poisonings although we have no knowledge of the number of cases occurring annually, since it is not reportable ' The enterotoxin is heat stable even

after boiling for 30 minutes and chlorine in palatable amounts is not effective in destroying it

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at 10 a m the day of the dinner and had been kept on the steam table until ready to use at 8 p m Two persons who ate the sauce at noon and a third who ate it between 5 and 6 p m were not made ill The department urges scrupulous cleanliness in preparing and handling hollandaise sauce and other foods of this nature Over 165 persons principally nurses and employees of a large upstate general hospital became ill with an explosive onset of gastrointestinal symptoms 6 hours after eating turkey salad The meat used had been left over from roast turkey served 48 hours previously Laboratory examination demonstrated a hemolytic *Staph aureus* in large numbers both in the salad and in the meat from which it was prepared Twenty persons, employees of an upstate industrial plant, became ill with nausea vomiting and diarrhea after eating cream meringue pie at the plant cafeteria The pies were approximately 18 hours old when the first person was served The manner in which the pies were infected was not determined

In Worcester Massachusetts 180 persons in a large war industry became ill with nausea vomiting chills and prostration following a meal in the plant cafeteria The same strain of *Staph aureus* was isolated from the throat of a food handler from the ham served the employees and from the vomitus of one of the patients The ham had been kept at 90° F for 4 to 6 hours in thermos containers The author has observed repeatedly the disruption of a war plant as a result of a food borne outbreak in th plant cafeteria or following a plant banquet

During July 1941, 71 cases of staphylococcal poisoning occurred in 19 families The source was found to be improperly pasteurized milk sold by two retail milk dealers An outbreak occurred in California in which there were 110 reported cases in 28 families The patients became ill after eating cream custard cakes from a single bakery The sanitary facilities there were highly inadequate giving ample opportunity for the ubiquitous staphylococcus to contaminate the custard

Two interesting outbreaks are reported from Hamilton Ontario Twenty one persons in 5 families ate a custard filled pastry purchased from a bakery All the employees of the bakery were examined carefully and cultures were taken *Staph aureus* was isolated from 4 employees from cream pie, lemon roll and vanilla slices and also from jam pails pastry bags and milk from a can in the bakery The same bakery was involved in another outbreak 2 months later, when there were 8 persons ill in 4 families The staphylococcus persisted in the nose and throat of the employees of the bakery for 3 weeks but was absent 6 weeks after the outbreak In 1941 Hamilton had another outbreak of staphylococcal food poisoning A butterscotch pie baked in the restaurant where it was served was incriminated Staphylococci were obtained from the pie the pastry

lag tip and the vomitus of a patient These strains and one isolated from the baker were found to be identical

Onset is rapid and occurs from 1 to 5 hours after ingestion of the contaminated food The symptoms are dizziness nausea abdominal cramps and vomiting lasting usually only a few hours but in severe cases several days The temperature usually is normal the pulse is increased and frequently there are cold sweats Diarrhea may occur simultaneously with the vomiting or be delayed for several hours Patients may become markedly dehydrated (In an autopsy on a patient who died from acute staphylococcal food poisoning the outstanding finding was an extensive and marked lack of body and tissue fluids an adequate fluid intake might have saved the patient s life) The acute symptoms generally last only a few hours but in severe cases there is prostration and recovery may be delayed for several days During this period a temperature of 100° F is not unusual In salmonella infections the onset usually is delayed for twelve hours or more and fever is not an uncommon finding These are the two most important characteristics whereby staphylococcal food poisoning can be differentiated from salmonella infection

The treatment is symptomatic and in severe cases is essentially that of shock and dehydration which may become quite marked There is no specific therapy

The differentiation of staphylococcal and salmonella food poisoning is important in the control of the outbreak and in the treatment of the patient In the former the incubation period is short usually 2 to 4 hours and the onset is characterized by abdominal cramps or pain nausea vomiting and diarrhea Fever is not a usual finding The duration averages 6 to 8 hours and recovery is rapid In salmonella infection the incubation period is 6 to 24 hours and fever is common The duration is much longer and recovery is delayed for days Slocum states that salmonella infection is commoner in Europe than staphylococcal food poisoning whereas in the United States the reverse holds true

Chemical Poisoning

Food borne chemical poisoning is comparatively rare as contrasted with staphylococcal food poisoning However the clinical syndromes of these two types are closely similar Both are characterized by a short incubation period The onset of nausea vomiting and diarrhea is sudden Sweating abdominal cramps and a normal or subnormal temperature are characteristic in both In cadmium or fluoride poisoning the incubation period usually is somewhat shorter The only way however to distinguish between these two food poisonings is by analysis of the vomitus and the suspected foods The chemicals most likely to be found in food are fluorine cadmium arsenic and chemical refrigerants such as

methyl chloride escaping from defective mechanical refrigerators Dack lists the various chemical poisons and the characteristics of the gastrointestinal upsets that follow their ingestion

In Massachusetts an outbreak was traced to a discharged employee who added sodium fluoride insecticide to corn meal batter in a grudge against his employer There were no fatalities Lidbeck and associates[44] describe an acute sodium fluoride poisoning involving 263 cases and 47 deaths in a mental hospital in Oregon Sodium fluoride was added to scrambled eggs by a patient who confused a barrel of sodium fluoride an insecticide, with one of powdered milk Many of the inmates did not eat the eggs because of the bad taste The incubation period was short, the chief symptoms being nausea vomiting and diarrhea leading to collapse Where patients were ill over a longer period of time the pupils became dilated the pulse was thready respirations were shallow and unlabored, the heart tones were weak and the skin was cold moist and cyanotic Other symptoms were paralysis of the muscles of deglutition, carpopedal spasm and spasms of the extremities

In a New York reform school[3] 69 of 96 persons who ate chocolate pudding for dessert suddenly became ill with nausea followed by repeated vomiting severe cramplike pain in the epigastrium and later by one or two loose movements Weakness and sweating were prominent symptoms Headache, salivation and lacrimation were present The temperature was normal or subnormal Investigation revealed that an inmate kitchen helper had added a handful of roach powder containing sodium fluoride to one hundred gallons of chocolate pudding The amount of sodium fluoride varied in different samples of the pudding ranging from 0 1 to 0 3 per cent Since a serving consisted of 200 gm of pudding each patient ate 0 2 to 0 6 gm of sodium fluoride an amount that is below the lethal dose of 3 gm Legislation has been passed in New York State requiring the coloring of all fluoride containers and insecticides by prescribed dyes Similar requirements should exist in all states

Recently cadmium poisoning has become prevalent as a result of the replating of metal food utensils with alloys containing this metal In New York between 1938 and 1941 4 outbreaks of cadmium poisoning occurred, 3 of these from acid foods prepared in cadmium plated food utensils and 1 from ice cubes in a cadmium plated tray in a leaky refrigerator where the escaping refrigerant dissolved some of the cadmium As a result of these outbreaks the use of cadmium in the replating of food utensils is no longer permitted in New York

Cangelosi[46] describes 3 outbreaks with 208 cases in the Fleet Marine Force operating in the Caribbean in 1941 The principal findings were abdominal pain nausea, vomiting, normal or subnormal temperature sweating and headache Recovery was rapid All the patients drank coffee or lemonade made in cadmium

plated containers Treatment consisted of the administration of warm water to encourage emesis and for those more severely ill bismuth subnitrate and paregoric to control diarrhea Measures were instituted to stop the use of cadmium in metal food containers Fifty cases in 5 other outbreaks were reported due to drinking an acid liquid prepared in cadmium plated containers

Several outbreaks of similar food poisoning occurred in a number of hotels in the same area Investigation revealed that the e institution were using the same brand of silver polish which analysis showed to contain sodium cyanide This chemical can no longer be used in silver polish in New York

The use of insecticide or spray on fruits and vegetables carrie a distinct danger because the chronic effects of continued ingestion of the lead arsenic or fluorine in the liquid may result in illness Prevention of this poisoning Cangelosi states may be achieved by requiring that fruits be acid washed or trimmed or otherwise conditioned so that they will reach the wholesale and retail markets with a legal tolerance of 0 05 gr of lead 0 025 gr of arsenic and 0 02 gr of fluorine per pound The cooperation of growers shippers and food inspectors is required in order to prevent chronic poisoning from insecticides and spray residues Scott[47] discusses a case of arsenical hepatitis from spray residue on fruits and vegetables Sampson[4] describes an outbreak of polyneuritis in South Africa due to the ingestion of triorthocresyl phosphate contained in cooking oil

Shellfish Poisoning

A paralytic form of shellfish poisoning has been reported along the Pacific coast of the United States and Canada The same type of disease has been reported from Nova Scotia eastern Canada and Belgium The poisoning is due to the presence of the dinoflagellate *Gonyaulax catenella* The warm sun and the cold nutrient waters along the Pacific Coast are responsible for an abundance of this organism in the summer The poisoning is due to an alkaloid that is heat stable in acid or neutral solutions but is gradually destroyed by boiling in alkaline solutions One millionth of a gram is lethal for a mouse and a few milligrams for man The alkaloid is stored in the digestive glands of mussels and excreted over a period of weeks The poison is not stored in the muscular tissue of the mussel Ocean mussels and large varieties of clams on the West Coast including the Washington and pismo types have been incriminated Since 1927 there have been 346 cases and 4 deaths from mussel and clam poisoning along the Pacific Coast from Alaska to Mexico all the cases occurred between May 15 and October 15 In July 1936 there was a mussel poisoning outbreak in Nova Scotia with 2 deaths The symptoms begin immediately after the mussels are eaten A prickly feeling in the extremities and tongue is followed by numbness An ataxic

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cern of the Engineering Section Committee of the American Public Health Association which publishes periodical reports on sanitary procedures including standards for disinfection of dishes and utensils evaluation of dishwashing machines detergents and other aspects of food sanitation

Municipal health departments are the chief agents responsible for the sanitation of food establishments The primary objective of food establishment inspection is the prevention of food poisoning and infections transmitted by foods This entails the cooperation of the entire food industry Training of commercial food handlers is an accepted method of developing safe and sanitary procedures in restaurants and other food handling establishments Many municipalities have developed such courses In Texas the state has assumed this responsibility by means of itinerant instructors and is convinced that the training is effective in improving the sanitation of establishments

The elimination of unhealthy animals is one of the veterinary s contributions to the control of the e diseases Veterinaries list 46 causes for which meat may be rejected or condemned as unfit for human consumption The public health engineer or inspector can do much to track down the mode whereby food may have become infected during processing and take necessary measures to prevent a repetition The ordinances regulating food and drink establishments as recommended by the United States Public Health Service or regulations based on it have been legally adopted in 74 counties and by 123 municipalities in 19 states These regulations provide minimum standards for the operation of a licensed or graded food handling establishment Inspection of all restaurants is required at least once every 6 months If violations of regulations are not corrected after notice in a reasonable time temporary suspension of the license or degrading (publicly displayed) and if necessary hearings court action and fines are the methods of enforcement

Regulations applying to food handling establishments must be rea onable and practical and must be enforced simultaneously with the education of the food handlers In the hand washing of dishes temperatures of 120 F for the wash water and 170 F for the rin e water thermostatically maintained are considered adequate Enough detergent must be used to remove properly all types of materials in a short time Soap alkali pho phates silicates and sulfated alcohols are some of the detergents evaluated by Gilcreas and O Brien Alkyldimethyl benzyl ammonium chloride is recommended by Krog and Marshall as an efficient sanitizing agent for the cleaning of eating and drinking utensils

The Food and Nutrition Section of the American Public Health Association surveyed ten public eating establishments to study the effect of an educational program and to evaluate methods Mechanical washing of drinking glasses and eating utensils is better than hand washing because standards are more easily

gait and muscular incoordination progress to ascending paralysis and death from respiratory paralysis in two to twelve hours Gastrointestinal symptoms are rare except in severe cases where there may be vomiting There is no known antidote Suspected shellfish should be packed in alcohol and sent to a laboratory for analysis

METHODS OF CONTROL

Health Department Responsibility

The control of food borne disease should be the concern not only of epidemiologists and other public health officials but also of all physicians food handlers and citizens who wish to bring the war to a rapid and victorious end Gastro intestinal diseases are a major cause of absenteeism in industry McGee and Cregar determined that 18 6 per cent of 40 942 days of work lost by employees of a powder company plant in New Jersey in 1941 were due to gastrointestinal disturbances Of 5 402 absences from work 24 per cent were due to this group of diseases Of the 7 605 days lost from diseases of the digestive tract 30 6 per cent were from gastrointestinal upsets and colon dysfunction and 4 1 per cent from enteritis and dysentery Most of the absenteeism occurred early in the week especially after week ends and after holidays

Food poisoning frequently disrupts large war plants Moreover the importance of dysentery among the military personnel cannot be overemphasized The health officer the industrial physician the industrial manager the food handler and the consumer himself play important roles in controlling food borne disease One of the roles of public health activity in the national emergency is to ensure the ordinary sanitation of safe water and milk supplies, protection of food supply and sanitary methods for excreta disposal

Health officers are expecting an increase in food borne disease acquired in public eating places as a result of the war More people are eating in restaurants because of the rationing of food and the placing of women in industry Increasing difficulties are being encountered in restaurants the lack of responsible personnel trained in the sanitary and proper handling of food, the overburdening of kitchen facilities the unavailability of proper equipment and in some cases short cuts and improper methods in food processing are the principal causes of the increase in food borne disease

Horwood and Pesare[51] made sanitary surveys of public eating places in Rhode Island and concluded that ignorance of accepted sanitary requirements and procedures as manifested by the managers and employees of public eating and drinking establishments is the most important single cause of insanitary practices in such places The development of accepted sanitary procedures has been a con

Control of Pastry Fillings

Since custard filled and cream filled pastries are one of the commonest vehicles for the transmission of food borne disease much research has been carried on in an endeavor to make these favorite items of the American diet safe for the consumer One of the methods for controlling the ubiquitous staphylococcus in such pastries is rebaking as described by Stritar Jungewaelter and Dack[5] Fifteen bakeries in Baltimore were using this procedure and finding it satisfactory The rebaking for fifteen minutes at 216 to 220° C (420 to 428 F) destroys staphylococci and has no effect on the palatability or appearance of the pastry Larger pastries should be rebaked for twenty minutes There seems to be no doubt that rebaking pastry will eliminate effectively a large proportion of food borne disease, for which pastry always has been a common vehicle Staphylococci and salmonella organisms, the two bacteria most frequently found will be destroyed thereby

Cathcart Ryberg and Merz have studied methods of controlling *Staphylococcus aureus* and *Salmonella enteritidis* by various methods Although ultraviolet light (2 000 to 2 950 angstrom units) effectively reduces the count of both organisms in the air and on smooth surfaces it does not penetrate the surface of custard products similarly ozone has proved to be ineffective Both methods produce an unpleasant odor after the prolonged exposure of custard filled pastry The growth of both organisms is effectively inhibited by the pH and the type of acid or other substances (lemon orange pineapple apricot and strawberry) present in pure fruit fillings if prepared by a special formula The addition of milk which may act as a buffer to a fruit filling reduces the inhibitory action If lemon juice and grated lemon rind are added to a standard custard there is no inhibition of growth until the concentration of these additions becomes so high that the product is unsatisfactory to the purchaser

Natural chocolate and natural cocoa fillings prepared by a special formula preferably without eggs have an inhibiting action on the growth of *Staphylococcus aureus* This effect seems to be due to the pH and to a combination of substances present in the non fat part of chocolate and cocoa Merely bringing custards to a second boil after the addition of the thickening mix renders them sterile to both *Staphylococcus aureus* and *Salmonella enteritidis* Use of these methods decreases the risk of poisoning

The utilization of special filling formulas the proper sanitary handling of products the boiling of custard or the rebaking of pastry and the rapid utilization of the product should decrease effectively the number of food borne outbreaks due to cream filled and custard filled pastries and prevent the occurrence of such serious outbreaks of poisoning as have appeared in the past

set the temperatures of the wash water and the rinse water are higher, and the procedure is more easily controlled If proper procedures in the hand washing of dishes are used and clean towels are available, the number of bacteria per utensil can be reduced

One of the most effective methods of reducing food borne disease is the enforcement of proper personal hygiene practices by all food handlers Strict enforcement of hand washing before handling food, and especially after visiting the toilet, will do much to reduce typhoid, salmonella and shigella infections These diseases usually are spread from the food handler s fingers that have been soiled by his excreta Keeping the hands away from the mouth and nose and covering the mouth while coughing or sneezing followed by washing the hands, covering foods whenever possible refrigerating those that are perishable, reducing the interval between cooking and eating, eliminating food handlers with purulent wounds boils or infections of the hands, preventing food handlers with sore throats from preparing food all these will reduce most of the chances of contamination

Examination of Food Handlers

The perennial question of routine examination of food handlers always appears In New York City the finding of each typhoid fever carrier by routine stool cultures of food handlers cost the city $50 000 therefore, the examination of food handlers was discontinued in 1934 Fort Worth undertook routine examinations of food handlers and expended $353 77 for finding each typhoid fever carrier The local medical society finally concluded that it did not favor routine medical examinations of food handlers, the same conclusion that was reached in San Francisco Most health authorities have now given up the recommendation of routine examinations of food handlers as impractical and as involving an unjustifiable expense of funds that could be utilized for more effective methods of food control

Consumer Control

An important person in the control of food borne disease is the consumer The buyer must be aware of what sanitary and insanitary food handling means in relation to health The health authorities must arouse in consumers a desire to trade in shops where food is handled in a clean and sanitary manner Public opinion is a powerful influence on the commercial food handler, the storekeeper will sell the buyer whatever he demands When the public is taught to demand safe clean and sanitary food properly processed and handled food borne disease will be reduced to a minimum

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CHAPTER XI-B

MILK SICKNESS

By MAJOR JAMES STEVENS SIMMONS, MEDICAL CORPS, U. S. ARMY

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Definition.—Milk sickness is a disease produced by the ingestion of milk or milk products from animals suffering with "trembles," a condition caused by grazing on certain poisonous weeds including the white snakeroot, *Eupatorium urticæfolium* and the rayless goldenrod, *Aplopappus heterophyllus*. Both of these plants contain a toxic chemical substance called tremetol, which is believed to be responsible for trembles in cattle and milk sickness in man.

Synonyms.—Milk sickness has been known by a variety of descriptive local names. In the eastern United States it has been called "milk sick," "sick stomach," "bilious sick stomach," "puking fever," "tires," "slows," "trembles," "river sickness," "swamp sickness," "fall poison," and "white snakeroot poisoning." In the southwest the terms "milk sick" and "alkali disease" have been commonly used.

After eating either white snakeroot or rayless goldenrod, certain lower animals including horses, sheep and cattle may show symptoms of trembles within two or more days. These symptoms include anorexia, thirst, constipation, extreme weakness, restlessness, staggering gait and violent trembling of the voluntary muscles, followed by paralysis. The breath is fetid and usually has a strong odor of acetone. Coma and death may follow after three or more

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days depending on the cumulative action of the poison Even after apparent recovery any unusual exertion may cause a recurrence of symptoms and a fatal termination It has been claimed that in lactating animals the symptoms are less severe because of the elimination of the toxic agent through the milk The ingestion of milk from such animals results in milk sickness which, in man, is characterized by symptoms resembling those of trembles The mortality has been estimated at twenty five per cent However, the disease is now less important than formerly, because of the marked decrease in its prevalence

History and Distribution

Milk sickness has been recognized in the eastern portion of the United States during the past century and a half It was reported in North Carolina before the American Revolution and it added to the trials of the early settlers in many localities west of the Appalachian Mountains and east of Missouri At times milk sickness completely wiped out small frontier settlements, and it is claimed that this mysterious disease caused many families in Tennessee, Kentucky and elsewhere to migrate to new locations

Geographically the distribution of the disease has been limited to places favorable to the growth of the causative plants As white snakeroot is found from Minnesota to Louisiana and as far east as North Carolina both trembles and milk sickness have occurred in this section Most of the outbreaks have appeared during the late summer or autumn months at which time the usual supply of wholesome plant food may be scarce, and the weed grows most luxuriantly Apparently white snakeroot is not palatable to cattle, and the animals usually will avoid it except when extremely hungry As the plant develops best in moist woodlands along creek bottoms and rivers, the disease was encountered more commonly during the early period, before the extensive clearing of the forests and cultivation of the virgin soil White snakeroot still grows along many streams of the eastern Mississippi valley, including Illinois Indiana Ohio Kentucky Tennessee and the southern part of Wisconsin It is also found in Iowa Missouri Arkansas Mississippi Alabama, Georgia and in the Carolinas Milk sickness due to this plant is reported occasionally in these states but as the disease usually is limited to isolated farms or to small rural communities it seems probable that a large percentage of the cases are not recognized

The first white settlers in the Pecos valley of New Mexico and Texas also encountered milk sickness which they called alkali disease Although caused by a different plant the rayless goldenrod the symptoms in both man and the lower animals appear to be identical with those produced by white snakeroot in the eastern states Rayless goldenrod has a wide range, extending from

southern Colorado to the Texas Panhandle and south into Arizona Sonora and *Chihuahua and is especially abundant in irrigated parts of the Pecos valley* The disease caused by this plant still occurs in the southwest but its incidence has decreased since the more general recognization of the etiological factor

The present incidence of milk sickness is unknown because of the lack of accurate statistical records However it is estimated that hundreds of cases still occur each year in the United States

Etiology

(a) *Milk Sickness in the Eastern United States* —At an early period in the history of milk sickness it became apparent that this disease was in some way related to the use of milk from cattle suffering with trembles However the cause of the latter remained in doubt for a long time during which many agents were suspected These included various unidentified microorganisms supposed to be present in stagnant water toxic minerals in the earth or poisonous emanations from soil decomposition products in hay poisonous mushrooms or other fungi and pathogenic bacteria particularly the *Bacillus lactimorbi* It has also been suspected that trembles might be due to feeding on poisonous plants including the white snakeroot In 1839 Rowe[1] performed a public experiment during which he fed this plant to cattle and produced symptoms typical of trembles He also reported the transmission of the condition through the cow s milk to a calf Vermilya in 1855 produced trembles in sheep and horses by feeding them on white snakeroot In 1867 Jerry[3] observed that the accidental ingestion of this plant prepared as greens was followed by severe symptoms identical with those of milk sickness The work of Moseley[4] 1906 showed that extracts of white snakeroot had poisonous properties which he later attributed to an ether soluble resin and he too was convinced that the *plant produced trembles in animals and milk sickness in man*

On the other hand Crawford in 1908 concluded that white snakeroot was not toxic and was therefore unrelated to the disease His paper was followed in 1909 by the comprehensive report of Jordan and Harris whose work suggested that milk sickness might possibly be due to an organism of soil origin called *B lactimorbi*

It has since been shown that sterile preparations of white snakeroot including extracts of the plant can produce trembles and the extensive experiments of Brooks[7] Clay[8] Marsh and Clawson[9] Curtis and Wolf[11] Wolf Curtis and Kaupp[1] Sackett[13] Couch[14] and others have proved the etiological importance of this weed Couch in 19 7 reported the isolation from white snakeroot of a toxic substance tremetol with which he produced trembles experimentally and which is now accepted as the cause of milk sickness

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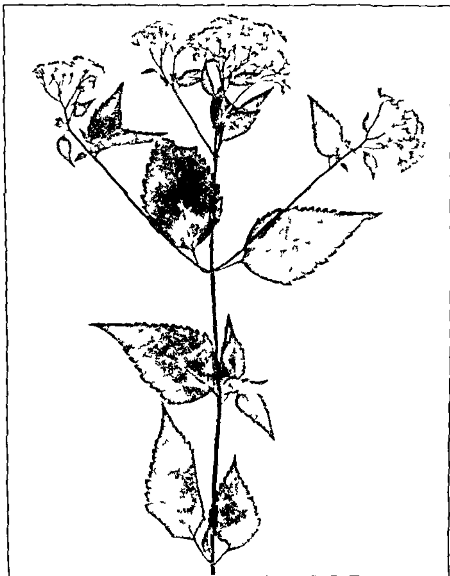


Fig 2 — White snakeroot or richweed (*Eupalor um url cæfolium*) (Photograph by Bureau of Animal Ind stry U S Department of Agriculture)

White snakeroot – Eupatorium urticæfolium Reichard, (E ageratoides, L), also called white snakeroot richweed, polewort, squawweed, or boneset,[4] is a slender erect perennial herb of the family, Compositæ The plant grows to a height of one to four feet Its leaves are opposite, three to five inches long

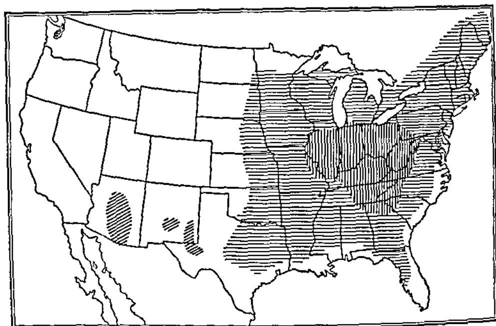


FIG 1 — Distribution of milk sickness in the United States 1930 Eastern type Western type Distribution of white snakeroot (Furnished by the Bur Animal Industry U S Dept of Agriculture)

broadly ovate and pointed with sharply toothed edges The leaf stalk is one fourth to one half the length of the leaf The small white flowers appear late in the summer and fall in compound corymbs of eight or more flowers The plant grows best in the rich soil of damp woods is especially abundant in groves along the streams of the middle section of the United States and in the coves or shaded ravines of the northern slopes of the southern Appalachians Although it does not develop so well in bright sunlight and usually disappears when the shade is removed it may appear in cleared pastures *Eupatorium serocinium* another of the forty species of white snakeroot in the United States has also been suspected as poisonous but *E urticæfolium* is the only species of this genus incriminated as the cause of trembles and milk sickness

(b) *Milk Sickness in the Western United States* — In 1909 Jordan and Harris[6] observed that the so called ' alkali disease ' of the southwestern United States was clinically indistinguishable from the milk sickness and trembles of

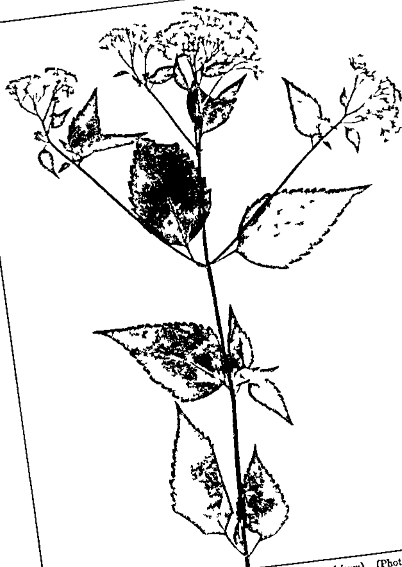


FIG 2 — Wh te snakeroot or nchweed (*Eupatorium urticæfolium*) (Photograph by Bureau of Animal Industry U S Department of Agriculture)

the eastern states For some time it has been suspected that alkali disease might be due to a local weed the rayless goldenrod Marsh, Rowe and Clawson[10] 1926, by feeding this plant to animals produced typical symptoms of trembles and proved its importance In 1930 Couch[14] confirmed these observations and showed that tremetol, the toxic principle of white snakeroot is also present in rayless goldenrod

Rayless goldenrod – Aplopappus heterophyllus (Gray), Blake, (*Isocoma wrightii*), also called rayless goldenrod or jimmy weed is a member of the composite family It is a stout erect tufted perennial herb one to four feet high depending on the amount of available moisture The leaves are alternate and linelike one eighth to one fourth inch wide and three fourths to two and one half inches long often with stiff hairs on the margin occasionally with short sharp irregular indentations and either acute or obtuse at the apex Flowers are produced in compact heads as in the case of sunflowers and each head has seven to fifteen tubular yellow flowers The heads are numerous with or without stems in terminal flat topped bunches and the bracts surrounding the flower heads are oblong usually obtuse with faint green tips and about one eighth inch high



Fig 3 — Rayless goldenrod (*Aplopappus heterophyllus*) (Photograph by Bureau of Animal Industry U S Department of Agriculture)

Another species A *frusticosus* (Rose and Standley) Blake, which grows abundantly in Arizona has a toxic action reported as similar to that of A *heterophyllus*

Tremetol — According to Couch[14] tremetol is an aromatic, optically active straw yellow oil of the composition $C_{16}H_{22}O_3$ It is not very stable, and it cannot be distilled without decomposition even in high vacuum but it is not destroyed at the temperature commonly used for the pasteurization of milk Tremetol is readily oxidized in the presence of air and disappears rather rapidly during the storage of dried plants For some unexplained reason this loss of tremetol due to drying appears to be slower in the case of rayless goldenrod Dried white snakeroot which has become free of tremetol, may still be dangerous

because of a remaining toxic resin acid but it fails to cause trembles Tremetol is insoluble in water acids and alkalies but is readily soluble in fats and fat solvents Couch therefore concludes that it is probably excreted in milk and might be present in butter made from such milk However due to lack of suitable specimens for examination tremetol has not yet been isolated from milk and the question remains as to whether it may not be excreted in a modified but still toxic form When fed experimentally to sheep tremetol produces the characteristic signs of trembles

Couch's Test for Tremetol Couch has used the following method for the detection of tremetol in plants The suspected material is extracted with petroleum ether Ordinary gasoline may be used if it does not give a red color with sulphuric acid The solution is poured on the surface of c c of concentrated sulphuric acid in a dry test tube when if tremetol is present a red color appears at the junction of the two layers Upon shaking the tube the petroleum ether layer is colored a transient red and on allowing the layers to separate the lower layer of acid is colored a fine cherry red while the upper layer is colorless If the solution is very dilute only an orange color will result

Although other substances may also give a positive reaction with this test it is believed that they are not likely to be present when tremetol is suspected and that foods reacting in a positive manner should be regarded as probably dangerous

Pathology

The pathological changes characteristic of trembles in lower animals have been described by Jordan and Harris[6] as follows One of the main lesions found in the post mortem examination of cattle is fatty degeneration of the liver which often is very extreme The small intestines usually are empty except for a tenaceous yellow mucus In some instances hyperplastic areas are noticed in the intestinal walls and occasionally small hard nodules are found The mesenteric glands often are enlarged The kidneys show as a rule cloudy swelling or fatty degeneration We have found no involvement of the central nervous system The heart muscle often shows fatty degeneration sometimes in slight sometimes in marked degree Ecchymoses in the wall of the heart on the liver and occasionally on the spleen are observed The voluntary muscles do not seem affected Knowledge concerning the pathological lesions of milk sickness in man is based on a small number of observations but the available reports indicate that the changes are essentially similar to those found in cattle Walsh[15] (1909) reporting the post mortem findings of a case examined in 190 stated that all the organs were found to have undergone fatty degeneration especially the liver and pancreas In additional cases examined

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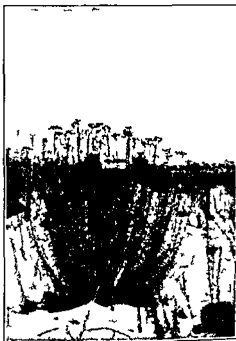


Fig 3 — Rayless goldenrod (*Aplopappus heterophyllus*) (Photograph by Bureau of Animal Industry U S Department of Agriculture)

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Tremetol — According to Couch[14] tremetol is an aromatic optically active straw yellow oil of the composition $C_{16}H_{22}O_3$ It is not very stable and it cannot be distilled without decomposition even in high vacuum, but it is not destroyed at the temperature commonly used for the pasteurization of milk Tremetol is readily oxidized in the presence of air and disappears rather rapidly during the storage of dried plants For some unexplained reason this loss of tremetol due to drying appears to be slower in the case of rayless goldenrod Dried white snakeroot which has become free of tremetol may still be dangerous

because of a remaining toxic resin acid but it fails to cause trembles Tremetol is insoluble in water acids and alkalies but is readily soluble in fats and fat solvents Couch therefore, concludes that it is probably excreted in milk and might be present in butter made from such milk However due to lack of suitable specimens for examination tremetol has not yet been isolated from milk and the question remains as to whether it may not be excreted in a modified but still toxic form When fed experimentally to sheep tremetol produces the characteristic signs of trembles

Couch's Test for Tremetol — Couch has used the following method for the detection of tremetol in plants The suspected material is extracted with petroleum ether Ordinary gasoline may be used if it does not give a red color with sulphuric acid The solution is poured on the surface of c c of concentrated sulphuric acid in a dry test tube when if tremetol is present a red color appears at the junction of the two layers Upon shaking the tube the petroleum-ether layer is colored a transient red and on allowing the layers to separate the lower layer of acid is colored a fine cherry red while the upper layer is colorless If the solution is very dilute only an orange color will result

Although other substances may also give a positive reaction with this test it is believed that they are not likely to be present when tremetol is suspected and that foods reacting in a positive manner should be regarded as probably dangerous

PATHOLOGY

The pathological changes characteristic of trembles in lower animals have been described by Jordan and Harris[8] as follows One of the main lesions found in the post mortem examination of cattle is fatty degeneration of the liver which often is very extreme The small intestines usually are empty except for a tenacious yellow mucus In some instances hyperplastic areas are noticed in the intestinal walls and occasionally small hard nodules are found The mesenteric glands often are enlarged The kidneys show as a rule cloudy swelling or fatty degeneration We have found no involvement of the central nervous system The heart muscle often shows fatty degeneration sometimes in slight sometimes in marked degree Ecchymoses on the wall of the heart on the liver and occasionally on the spleen are observed The voluntary muscles do not seem affected Knowledge concerning the pathological lesions of milk sickness in man is based on a small number of observations but the available reports indicate that the changes are essentially similar to those found in cattle Walsh[13] (1909) reporting the post mortem findings of a case examined in 1902 stated that all the organs were found to have undergone fatty degeneration especially the liver and pancreas In additional cases examined

by Walsh[15] and in several by Jordan and Harris[6] extreme degeneration of the liver and in some instances of the kidney were noted, but no mention was made of any unusual involvement of the pancreas

Symptoms

Trembles in Cattle

The period required for the development of symptoms of trembles may vary from two days to several weeks depending upon the amounts of tremetol ingested and the intervals at which the poisonous plants are eaten The fir t signs of the disease are weakness and a disinclination to exertion The animal s head and ears droop and it walks with a hesitating staggering gait, unable to keep pace with its companions During its frequent stops the animal may attempt to defecate, but as a rule this effort is unsuccessful because of constipation There is extreme muscular weakness, particularly of the front legs, and any exertion may bring on the characteristic trembling from which is derived the name of the disease If such an animal is driven it usually falls, lies panting unable to rise and may die in a short time In certain localities where trembles was prevalent it was once the custom of cattle buyers to exercise the animals before their purchase in order to detect those in the early stages of the disease Restlessness and increased excitability have been observed during this early period If the disease progresses, exhaustion becomes more pronounced and the animal becomes prostrated often lying with the front legs flexed and the hind legs extended After this stage s reached many cows die but recovery may occur If there is no improvement the animal becomes weaker and lies on its side often with the neck outstretched and the head bent back The eyes are injected and there is a yellowish red gummy discharge There may be clonic convulsions of the muscles particularly of the forelegs The temperature usually is subnormal while both pulse and respiration are irregular The latter develops a Cheyne Stokes rhythm as consciousness is lost shortly before death As a rule the animal is constipated throughout the entire illness Aside from the trembling of the muscles one of the most constant findings in trembles is the acetone odor of the breath This is usually more apparent as the disease progresses According to Couch the poisoned animals suffer from a ketosis Acetone has been demonstrated in the urine and blood as well as in the air expired from the lungs

The symptoms vary in severity among different individuals of a single herd It has been claimed that milk cows may show little or no evidence of the disease so long as they continue to eliminate the toxin through the milk but if lactation stops such an animal will usually develop typical symptoms

Milk Sickness in Man

Preliminary Stage — After a variable period depending on the amount of poison in the milk and the frequency with which it is taken the disease may appear in subacute or acute form In either case there is a preliminary stage characterized by lassitude and general weakness which gradually increase At about the same time dull pains may be felt in the calves of the legs and in some cases in the thigh muscles Headache may or may not be noted The appetite always is impaired and all desire for food may be lost This is accompanied by gastric discomfort which usually is relieved by eating Constipation is extreme The patient is inclined to be sleepy Any exercise during this stage is detrimental and soon is followed by nausea If the patient lies down the vomiting characteristic of the disease may be delayed This first stage of milk sickness may last from two to ten days to be followed by recovery it may continue for a much longer period passing gradually into the subacute or chronic form of the disease or it may be rapidly followed by the acute form

Subacute Form – The subacute form which often lasts for many months has been known by the appropriate term lows The patient is languid and is unable to exert himself either mentally or physically The appetite is variable and most patients suffer with constipation There may be some stiffness of the limbs with cramps in the calf muscles Palpitation of the heart is not uncommon Both the pulse and respiration rates are irregular the temperature is subnormal and the systolic blood pressure is low Physical exertion or unusual delay in the time of taking food may result in trembling and nausea followed by vomiting The patient loses weight rapidly the skin becomes wrinkled and may have a yellowish color The tongue is swollen clear red and tremulous Eye and knee reflexes are normal The liver is enlarged The breath is fetid and often has the odor of acetone The urine may contain a trace of albumen and a considerable amount of acetone This form of the disease may be followed by recovery passing gradually into a long period of convalescence during which the patient remains weak and may have frequent attacks of trembling If such an individual attempts to run the adductor muscles relax resulting in a staggering gait and a fall Over exertion or over eating at any time throughout the disease may bring on a severe acute attack followed by death within one or more days

Acute Form – When the acute form develops within two to ten days after ingestion of the toxic milk the preliminary stage of anorexia and weakness is followed rapidly by faintness prostration severe nausea and pernicious vomiting The stomach contents may be bile stained and usually have the odor of acetone The vomiting may be almost continuous for several days resulting in intense thirst and exhaustion followed by restlessness mental dullness and loss of con

sciousness Constipation is a characteristic symptom throughout the disease The abdomen which is scaphoid may become distended and painful The tongue is red and may become sore, dry and fissured The pulse rate may be as low as 70 or as high as 120 The temperature is usually subnormal and is rarely higher than 99° F The systolic blood pressure is low, from 95 to 105 and may fall as low as 57 The respirations are irregular As the disease progresses there may be pain in the calves of the legs, followed by stiffness The patient lies on his back with the head turned sidewise and the knees drawn up Hiccough is not infrequent the tongue may be tremulous Tendon and pupillary reflexes may be normal or sluggish The conjunctivæ are reddened and there is a gummy, yellowish discharge The liver is enlarged and may extend from 2 to 4 5 cm below the margin of the ribs Convulsive seizures may occur In some cases there is active delirium The breath is fetid and usually has a strong odor of acetone In fatal cases a period of coma precedes death which occurs in from one day to two weeks

Diagnosis

The diagnosis of milk sickness usually depends on the exclusion of other conditions that might cause the typical symptoms supported by a history indicating that the patient has used milk or its products from animals suffering with trembles If any of the suspected dairy product is still available, it should be tested for tremetol by the method of Couch as this may help to establish the diagnosis

Clinical laboratory examinations of pathological materials may also assist in the diagnosis but as the disease is limited to isolated rural communities relatively few cases have been thoroughly investigated by modern laboratory methods and therefore information on this phase of the subject is incomplete

The available data indicate that numerically the leukocytes remain within normal limits The vomitus and feces are acid and usually have the odor of acetone The urine is reduced in amount acid in reaction, with a specific gravity of from 1 020 to 1 030 and usually contains a trace of albumen It does not contain sugar but diacetic acid and acetone usually are present especially during the acute stage of the disease

It also appears that changes in the blood sugar may be associated with the development of acute symptoms Walsh[1] has reported that in three of four cases the blood sugar was slightly reduced in amount while in the other it was normal and he indicated that as these observations were made following the therapeutic administration of glucose, they probably do not represent the degree to which the blood sugar may be reduced under natural conditions Couch[14] during his experimental work with sheep fed on tremetol emulsified in syrup of

acacia observed that symptoms of severe poisoning appeared at least 24 hours before acetone was detected in the urine or on the breath and that the sugar content of the blood which decreased steadily following the feedings increased sharply during the period of severe illness Bulger Smith and Steinmeyer[16] from experiments with rabbits concluded that after feeding white snakeroot there is a ketosis a lipemia and a tendency toward a profound hypoglycemia. Walsh[15] in a recent discussion of milk sickness suggests that the poison absorbed from the milk or butter may have a special affinity for the liver resulting in typical fatty degeneration and in a disturbance of its power to store glycogen also that this condition may exist without severe symptoms until some unusual exertion depletes the dextrose remaining in the body and that since the normal reserve is already reduced this results in a condition of extreme hypoglycemia It appears that additional studies on this subject are indicated

Prognosis

Certain of the early observers estimated the mortality due to milk sickness to be as low as 2 per cent of the entire number of persons attacked or about 5 per cent of those who called for medical attention Others considered the mortality to be 10 per cent or higher and Collins[17] reported that about 40 per cent of his cases died In 1909 Jordan and Harris[6] analysed the records of twenty five observers published between 1829 and 1908 The mortality varied from 0 to 100 per cent and among the total of 318 cases there were 75 deaths a mortality of [illegible]0 per cent However they suggested that if mild or abortive cases are considered the mortality is probably not more than 10 per cent Hull[18] (1930) states that the mortality is about 25 per cent

In the acute form of milk sickness death may occur within a very few days and in the subacute form it may rapidly follow any unusual strain or exertion

Treatment

The treatment recommended for milk sickness was for a long time limited to complete rest in bed liquid diet and an attempt to eliminate the toxic materials by the administration of liquids in large amounts and the use of laxatives or enemata In 1908 Walsh[1] observed that during the acute stages of the disease there is a severe acidosis and demonstrated the therapeutic value of alkalies His method published in 1930 was as follows The treatment consists of neutralizing the diacetic acid in the blood stream and supplying dextrose The first thing given in all cases is an enema of one ounce (30 gm) of soda bicarbonate with two ounces (60 c c) of Karo syrup 85% glucose to the pint of warm water repeated every four hours If it is a severe case we give dextrose

by the vein and in the two cases that we have used it, we gave 50 c c of the 50 per cent solution of dextrose U S P , every hour, at the same time continuing with the soda and glucose by the bowel By mouth give one dram (4 gm) of soda bicarbonate and one (4 c c) of milk of magnesia in a glass of pop or water with one teaspoonful of Karo syrup every two hours, alternating with orange juice or skimmed milk

For nausea and vomiting every two hours we give a powder which contains cerium oxalate bismuth subcarbonate and chalk, until relieved, either with the soda or alternating with soda If I were called to a patient who was semi comatose with milk sickness I would wash out the stomach with solution of bi carbonate of soda and give one tablespoonful of bicarbonate of soda and two tablespoonfuls of glucose to a pint of water and leave it in the stomach The patient is so dehydrated that they absorb a lot of water in the first twenty four hours Soda is kept up till urine is alkaline "

Bulger[16] from observations on animals poisoned with white snakeroot, stated that the administration of dextrose was followed by rapid disappearance of the acetone and marked improvement If this was followed by a carbohy drate diet the animal was rapidly restored to health

Rest is of great importance throughout the disease, and even during the long period of convalescence patients should be impressed with the danger of strenuous exercise It is also essential that use of the suspected dairy products be discontinued

Prophylaxis

The prevention of milk sickness depends on the prevention of trembles in cattle or the avoidance of dairy products from affected cattle

Herds may be protected against trembles by the elimination of white snake root or rayless goldenrod from pasture lands In certain instances, badly infested areas have been enclosed with fences Cultivation of the land and planting corn grain or grasses will eliminate the weeds to a large extent How ever the most effective method is to remove and destroy the poisonous plants Education of the public in this matter already has resulted in a satisfactory decrease in the prevalence of the disease

Milk from animals affected with trembles is not rendered safe by pasteuriza tion However under the market conditions prevailing in the larger towns and cities such milk is sufficiently diluted with wholesome milk to render it harmless

Since milk sickness remains a problem of rural communities its future prev alence will depend on the education of the farmer concerning its dangers, cause and prevention

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CHAPTER XII

TUBERCULOSIS

By J. Burns Amberson, Jr.

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Recorded in the earliest annals of history and proved to exist in prehistoric times by the finding of lesions in unearthed skeletons tuberculosis stands today one of the most ancient and deadly of the enemies of man The earliest writings identify it by its lite and most prominent external characteristic wasting hence the names phthisis consumption and many others in different languages relating to the same symptom While tubercles and ulcers of the lungs were known among the ancients the nature relationships and developmental phases of the lesions were not revealed before the seventeenth and eighteenth centuries and then but slowly through the studies of Franciscus Sylvius Richard Morton

Thomas Willis Morgagni Pierre Desault Bayle and Mathew Baillie The classic studies of Laennec (1781–1826) dispelled the then prevailing idea that phthisis is a disease of many origins verified its unity and established clinical procedures which proved epochal Contagiousness of the disease was suspected in the fifteenth century by Fracastoro of Verona but proof of transmissibility had to wait for the work of Klencke (1843) in the case of bovine tuberculosis and for that of Villemin (1865) whose conclusive experiments demonstrated the specific infectiousness of the virus from human beings The identity of the bacillus *Mycobacterium tuberculosis* was settled finally in 1882 by Robert Koch The avian type of the organism was isolated in 1890 by Maguccі and the bovine in 1898 by Theobald Smith

Distribution

Tuberculosis is not confined alone to man It is found in practically all parts of the world and probably affects a wider range of animal species than does any other disease known to mankind Under favorable conditions this malady attacks all forms of wild and domestic animal life including mammals fowls fish and amphibians (Stiles) Wild animals appear free from the disease until kept in captivity Susceptible domestic animals are cattle and swine while goats cats sheep horses and dogs are affected much less often According to Scott disease caused by the avian type of bacillus is found most frequently among gallinaceous birds fowls pigeons pheasants quail guinea fowl and peacocks are liable to infection and in less degree turkeys ducks and geese Parrots canaries finches sparrows crows cowbirds and magpies may be victims Man is susceptible to infection by the human and bovine types infection by the avian type often with the development of skin lesions has been reported but seems to be rare at least in the United States (Feldman)

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losis as shown by Stiles is declining also with only 0 10 per cent of the carcasses coming under federal inspection condemned or sterilized in 1936

Occurrence in Man — The antiquity of human tuberculosis is evinced by the descriptions of the earliest medical writers In most of the world the disease was the major cause of death until the present century and in certain poorly developed countries as Alaska and Labrador it remains a primary if not the first cause In most of the civilized parts however there has been a steady decline in mortality from tuberculosis and there are good indications that this will continue perhaps at a slackening rate

Clinical consideration of tuberculosis must embrace the fact that the pulmonary form and its direct complications in adults account for more than 90 per cent of the deaths that children when affected suffer much more often from the generalized lympho hematogenous forms and that such clinical forms are phases of a complex but integrated pathological process Identification of the relationships between phases marks one of the important advances of recent years On another front studies of the peculiar behavior of tuberculosis as a social disease have revealed new and effective ways of dealing with the scourge necessitating intelligent action by the community This together with the development of improved diagnostic and therapeutic measures has made the physician a more indispensable leader and advisor than ever before in the campaign against tuberculosis

Morbidity and Mortality in Man — One of the most impressive changes in tuberculosis is the decline in mortality in fact some are so impressed as to consider the problem no longer a major one a view which is far from true Samuel G Morton reported the observation of Emerson that in 1820–27 one of every five to six deaths about 17 to 20 in every one hundred occurring in New York Boston Philadelphia and Baltimore were due to consumption in 1936 the ratio in New York City was 7 in one hundred among males and 4 6 among females In England and Wales the death rate has declined steadily from about 330 per 100 000 population in 1865 to 66 in 1937 in the United States from 202 in 1900 to 49 in 1938 Similar trends are reported from most well organized countries e g the mortality among males in the Netherlands dropped 57 per cent and among females 54 per cent between 1910 and 1930 (Rykels) while New Zealand claims possibly the lowest rate which was 39 per 100 000 in 1937 as compared with 75 in 1900 (MacIntyre) In the United States the rates are lowest in the middle west and highest in some of the south western health resort states Urban and industrialized sections usually

have high rates The figures collected by Drolet show the following rates per 100 000 population for certain cities in 1938 Baltimore 187 Boston 60 Chicago 60 Detroit 57 Los Angeles 72 Memphis 118 New Orleans 104 New York 58 Omaha 37 Philadelphia 66 Washington 98

While in most communities tuberculosis has yielded its preeminence as a cause of death to such conditions as diseases of the circulatory system cancer and pneumonia its destructiveness among certain groups of the population remains paramount Typical experiences may be cited as follows In New York City in 1936 tuberculosis was the leading cause of death in women between the ages of 15 and 34 and in men between 20 and 39 Twenty six per cent of all men and 34 6 per cent of all women who died between ages 20 and 24 died from tuberculosis The rate among negroes is in general two to three times that among whites but in adolescence is seven to eight times as high (Dublin) Tuberculosis in 1930 was the second cause of death among men aged 15 to 64 in the United States (Whitney) While the crude rate among infants and young children is comparatively low Drolet and others have shown that the rate calculated for infected infants may rise to 1 200 or more per 100 000 which is higher than that found in any other period of life Between the ages of 5 and 12 or 14 there are relatively very few deaths the reason as Landis stated why this period has been called the golden age Among people past 30 years of age the experience in many communities shows that more men than women die from tuberculosis the rate often being two to three times as high in the former after age 45 But in summary the mo t striking fact is that this disease remains the chief cause of death in the most productive period of life

The incidence of infection al o seems to be declining but at a much slower rate than the mortality In many urban communities it is still observed that 25 to 60 per cent of children in the high school age react to the tuberculin test while the rate rises clo e to 100 per cent among old adults (Keresztури and others) Of probably great significance is the decreasing infection of infants even among poor people as shown by the experience of Lincoln Raia and Gilbert at Bellevue Hospital Among 11 136 children tested between 1930 and 1936 the following percentage rather well distributed according to age reacted birth to 6 months 0 7 per cent 6 to 12 months 5 3 per cent 1 to 2 years 10 per cent 2 to 4 years 15 1 per cent 4 to 6 years 18 1 per cent 6 to 8 years 23 5 per cent 8 to 10 years 26 9 per cent 10 to 12 years 32 6 per cent Five times as many in the birth to six months group reacted in 1921–28 but the differences were very much less in the children

beyond one year of age In other sections particularly rural where the death rate is low the number of children who react to the test is be coming progressively less Soper and Amberson estimate that less than 50 per cent of the population of the United States below the age of 20 would react to the tuberculin test

Morbidity from tuberculosis is an unmeasured factor in most com munities In places where the disease is reportable as in New York City approximately two and a fraction new active cases are reported each year for each death thus in this city in 1938 there were 4 257 deaths and 9 742 new cases It is well known that this does not represent all the active tuberculosis in the community which has been estimated variously at 4 to 9 or 10 times the number of annual deaths Definitions of active differ Probably a closer approach to the fact is represented by the findings of x ray surveys of the chests of apparently healthy per sons Edwards reports studies of this type in more than 100 000 persons in New York City with the discovery that tuberculous lesions were found in 2 per cent of these in adolescent or adult life about one half the lesions being of clinical importance Fellows and his associates at the Metropolitan Life Insurance Company home office examined by fluoroscopy or roentgenograph 24 000 applicants for employment over 17 years of age in the period 1928–38 finding an incidence of demonstrable lesions in about 1 1 to 1 6 per cent of each year s groups Other studies have yielded rather similar figures and probably 1 to 2 per cent of the adults in most communities harbor demonstrable tuberculous lesions 50 per cent or more of which are obsolete and apparently arrested This incidence like that of tuberculin sensitivity has not declined like the mortality rate Fellows found about the same ratio among the applicants for employment in 1938 as he did in 1928

Causes of Tuberculosis

Tubercle Bacillus (Mycobacterium Tuberculosis)

This is the infective agent responsible for tuberculosis and is distin guished by its acidfastness that is the property of resisting decolorization after taking certain stains There are three well known types of the bacillus the human the bovine and the avian There is also a type which has been found to be capable of infecting cold blooded animals Other acidfast bacilli include *Mycobacterium lepræ* the grass bacillus the smegma bacillus and other non pathogenic types which sometimes are found in suppurative processes and have been called paratubercle bacilli

Non acidfast types or phases of the tubercle bacillus exist which are considered to represent early developmental stages These have been studied in recent years particularly by Kahn and Nonidez The bacillus as found in human cases is short solid and uniform for the most part Old cultures show longer beaded forms and these occasionally are found in the sputum of patients It is agreed generally now that the waxy constituents of the bacillus permeate its whole structure and do not exist as a capsule The bacillus grows readily in artificial culture media made up of various substances such as serum agar egg potato glycerol and meat juice oxygen is required It is more resistant than most bacteria to the action of various physical and chemical destructive agents Boiling for two minutes and pasteurization at 60° C kill tubercle bacilli Direct sunlight is said to kill them in suspension in ten minutes (Baldwin Petroff and Gardner) Dried bacilli protected from light are said to survive for four to forty weeks Under various artificial conditions the organisms may gradually lose their virulence and this occurrence has been shown occasionally also in lesions such as lupus of the skin (Griffith) Smithburn has been able to influence pathogenicity by altering the hydrogen ion concentration of the culture medium With very few exceptions strains of organisms obtained from human cases are uniformly virulent for guinea pigs Both the human and bovine types are pathogenic for man it is sometimes desirable to distinguish these which is accomplished by noting the cultural characteristics and the response of the rabbit to infection since this animal is not as susceptible to the human type as it is to the bovine The varying pathogenicity is shown in the following table of Stiles (Table I)

TABLE I

PATHOGENICITY

Bacillary Strains	Cavia	Rabbit	Fowl
Bovine	+++	+++	o
Human	+++	+	o
Avian	o	+++	+++

The Ways and Opportunities of Infection

Human tuberculosis is transmitted chiefly by the medium of contaminated air the source usually is a patient with open tuberculous cavities in the lung and a positive sputum He expels the organisms by coughing or other forceful respiratory effort and other people in the vicinity be

come infected by inhaling the fine droplets or particles with the air which they breathe Bacilli so inhaled probably seldom give rise to a lesion unless they gain access to the deeper parts of the lung Possible infection by way of the tonsils must be admitted but this is thought to be more usual when the infecting organisms are introduced in contaminated milk or other food The surfaces of the mouth nose pharynx trachea and bronchi seem to be relatively resistant to infection Ingested bacilli may cause lesions in the intestine and the related lymph nodes however it was found many years ago that animals withstand larger doses of tubercle bacilli introduced by ingestion than by inhalation (Cobbett) Other ways of infection are uncommon but there are isolated examples of inoculation through the skin acquired by pathologists butchers and others who handle tuberculous material A few bacilli, and sometimes even one bacillus inoculated subcutaneously into a guinea pig leads to generalized tuberculosis but there is reason to believe that the human being may withstand the introduction of a few into the body without the appearance of a lesion This is suggested by the frequent opportunity which some people have for such infections and the failure to find demonstrable lesions in their tissues Similarly a number of authors have commented on the failure of some children to develop a hypersensitiveness to tuberculin even though they may have been in contact with a tuberculous person for a considerable time The presumption is that the occasional inhalation or ingestion of a few bacilli may be followed by their prompt destruction or elimination through the action of the various natural defensive mechanisms The development of a lesion therefore implies that these mechanisms were impaired or inadequate at the moment of infection inadequate perhaps to cope with an unusually large dose of organisms

Natural Resistance Allergy and Immunity

A guinea pig successfully inoculated with the tubercle bacillus almost invariably develops generalized and fatal tuberculosis but a man seldom does Such varying susceptibilities exemplified in many members of the animal kingdom speak for great differences in natural resistance which obviously is developed to a high degree in man The nature of this is not clearly understood It fluctuates greatly under different influences There is no means of measuring it directly and it is estimated roughly only by observed reaction of the individual to the infection It seems queerly to change with age being low in infancy higher in childhood and depressed somewhat again in adolescence Likewise it seems to be a great factor

in determining whether a person after infection will develop clinical tuberculosis. A combination of a good natural resistance and the absence of unfavorable factors will prevent the occurrence of consumption. A combination of inherited low resistance and unfavorable factors is almost inevitably bound to lead to phthisis (Wallgren). In many and perhaps most instances natural resistance outweighs protection which may be acquired as specific relative immunity, and this raises the question of the effects of allergy and immunity.

With few exceptions the appearance of a tuberculous lesion is followed usually within three to eight weeks by the development in the tissues of specific hypersensitiveness, allergy, to the bacillus and its products. Such hypersensitiveness is manifested by the ability of tissues on contact with tuberculin to react with acute inflammation and also by the tendency for renewed infection with tubercle bacilli to be followed by a relatively more intense and more accelerated inflammatory reaction than would occur if this were the first infection. Furthermore, bacilli introduced into hypersensitive tissues are more likely to be localized at the point of inoculation and less likely to escape rapidly through the lymphatic and blood vessels to other parts of the body. Altered humoral and cellular reactions may have an inhibitory or destructive effect on the organisms (Lurie). This then is interpreted as an immune reaction. There has always been considerable confusion whether tissue hypersensitiveness and immunity represent substantially the same phenomenon or whether they are separable mechanisms. Krause and Willis and others hold the view that the two are closely interrelated and not wholly separable, while in recent years Rich and his co-workers have presented evidence showing that hypersensitiveness artificially may be reduced or almost entirely eliminated without, however, influencing specific immunity proportionately. Clinicians influenced by these fundamental conceptions have held, on one side, that the fate of humanity in regard to tuberculosis rests largely on protection by immunization from repeated small but universal infections, and on the other, that allergy is harmful to the tuberculous person since the reactions of intense inflammation and rapid caseous necrosis thereby are favored greatly. It seems to me that these factors, still not clearly understood, often are given more importance than they deserve and that in clinical practice one usually recognizes influences of more decisive effect such as natural resistance, racial susceptibility and many others of nonspecific character. It is difficult to assess opinion on this point since the question is still at issue, but it cannot be denied that small infections producing lesions which heal readily with little or no dissemination result in establishing a certain, perhaps small,

degree of relative immunity that tissue hypersensitiveness as a rule is not harmful and that in average conditions the factor of natural resistance with all that this implies is relatively of far greater importance than the other two This does not preclude that in some instances particularly in the progressive case of tuberculosis tissue hypersensitiveness may favor more rapid and harmful extensions of the disease

Other Etiological and Modifying Factors

Inheritance and *constitution* always have been considered to influence the liability to tuberculosis Instances of congenital and transplacental infection are so rare that they need not enter into the discussion The gradual reduction of tuberculosis in most civilized countries suggests that inheritance may have led to improvement of the racial resistance It is not possible to define clearly the constitution which represents good resistance Formerly the physical habitus represented by the long narrow chest the blonde complexion and the delicate skin and hair was interpreted to mean low resistance but there are numerous exceptions Weisman from anthropological measurements has come to the conclusion that a person with a flat chest is more likely to resist tuberculosis than one with a deep chest Certainly a robust constitution and vigorous general health are relative safeguards against the disease

The influence of *race* and *sex* appears in a somewhat more objective way The Jews have long been known to exhibit a relatively high resistance against tuberculosis and the reverse has been reported often among the negroes In the United States negroes in communities have a tuberculosis mortality rate three to five times that of the whites and Bushnell reports similar differences in various other parts of the world Another indication of the relative susceptibility of the negro is the more frequent occurrence in this race of the acute caseous forms of the disease and of lympho hematogenous disseminations Some have attributed these differences to social and environmental influences but the experience is too striking and observed too constantly to be related to these causes alone The greater susceptibility of girls during adolescence has been mentioned already

Environmental and *social economic conditions* are observed universally to have great influence People living under impoverished conditions especially if they are ill fed and ignorant are easier victims The opportunity for close contact with the open case under crowded conditions and the lowering of resistance on account of under nutrition seem to contribute to the hazard

Occupation directly or on account of its related social economic standard has an important bearing. In the statistics collected by Jessamine S. Whitney it is shown that tuberculosis death rates are lowest among men employed in the professions such as lawyers, bankers and physicians, rising steadily among less favored occupational groups until it is almost ten times as high among unskilled industrial workers. Occupations involving the use of silica in various forms and ways are especially hazardous. The development of silicosis definitely introduces an increased liability to tuberculosis, which is a major cause of death among exposed workers.

Physiological influences have been implicated frequently. The characteristic rise in the occurrence of and mortality from tuberculosis in adolescence strongly suggests that the changes of *puberty* are more or less responsible. Likewise *pregnancy* has been observed to have an influence in aggravating pulmonary lesions, and this may be important particularly when other conditions conspire to bring about a lowering of the natural resistance.

Intercurrent diseases sometimes play a part also. Among the most striking is diabetes mellitus. With diabetes the liability to tuberculosis is less than formerly, but as Root has shown there is still a definite susceptibility among young diabetics. The same is noticed in diabetics difficult to control. Circulatory diseases are said to influence the course of tuberculosis, but the alleged protective influence of mitral stenosis has been exaggerated; on the other hand, pulmonic stenosis is well known to favor the development of progressive and fatal tuberculosis. Arteriosclerosis and the attendant changes sometimes seem to open the way for the disease. The role of acute respiratory and other infections often is questioned. It cannot be denied that such debilitating influences, especially measles and grippe, may help lower the resistance, but in the individual case these factors usually are combined with others, and the connection, if any, is difficult to determine. Suppurative infections of the lungs when they lead to necrosis of the parenchyma occasionally cause the breakdown of old isolated and previously innocuous tubercles, and progressive tuberculosis may follow.

Trauma is being implicated with greater frequency, particularly since compensation laws have been passed in many localities. In my experience most of these claims have *not* been found to be justified, but occasionally the harmful influence of trauma is evident. The old theory that invasion of tuberculosis might be favored in traumatized tissues by the local lowering of resistance has found little to support it, and now it is invoked seldom. Usually the question is whether trauma has resulted in the

aggravation of preexisting tuberculous lesions and various mechanisms are suggested

Among those which sometimes prove detrimental are the following (a) Trauma of the chest wall seldom harmful to underlying tuberculous lesions may be so severe as to cause hemorrhage with bronchogenic dissemination of the infection (b) Trauma may be so severe as to cause rupture of the visceral pleura previously weakened by tuberculous lesions and the consequences such as tuberculous or mixed infection pyothorax may be immediately serious and eventually even fatal (c) Severe trauma may cause tuberculous pleurisy with effusion by causing the separation of pleural adhesions or the perforation of the pleura as by a fractured rib (d) It is conceivable that in a case of active pulmonary tuberculosis extension of the disease may be accelerated sometimes by the effects of a severe blow or contusion of the chest To determine such effects requires evidence preferably objective that unfavorable changes in the pulmonary lesions have come about within a few days or several weeks after the incident Otherwise unless the circumstances are very unusual the changes are ascribable more reasonably to the natural evolution of the disease

It is important therefore in such situations to insist upon a medical examination including x ray examination immediately after the trauma has occurred and at short intervals thereafter The possible influence of trauma upon other tuberculous lesions must be judged by similar criteria the close time relationship being important The effect of penetrating injuries of the chest such as gun shot wounds has not been found to favor the development of pulmonary tuberculosis unless diseased tissue is actually traversed by the missile an observation which has been discussed by Schulze

Contact with open cases of tuberculosis has to be rated a major cause of disease in others at least under certain conditions Contact in the home is important because of the intimacy and the opportunity for frequent repetition Infants and young children are especially endangered The possible danger for those working with patients in hospitals and sanatoria has received much study That nurses and medical students are infected frequently has been demonstrated but the likelihood of developing clinical disease has not been clearly estimated In some institutions the incidence of disease especially among nurses has been high while in others it has not exceeded that found in comparable groups not exposed to this hazard Accessory influences seem to enter into the picture and possibly play the major role in determining whether the exposed individuals will or will not develop the disease tuberculosis

PATHOLOGICAL FEATURES

While as indicated by the name tuberculosis a prominent feature is tubercle formation there are other lesions of equal importance As Laennec was able to distinguish the reactions to infection are represented on one hand by the formation of a grey tubercle and on the other by diffuse inflammation designated as infiltration While occasionally the reaction is exclusively of one or the other type as a rule the types are present in combination One organ may be involved with discrete grey tubercles while in another there are widespread infiltrations in which it is difficult to detect tubercle formation Lesions of different types may exist side by side in the same tissue and in other instances a recent and acute inflammation may surround well formed grey tubercles which were established at some previous time Pathologists since Laennec have all noted such distinctions and accordingly have built up varying conceptions

Laennec s fundamental observations of tubercle and infiltration have been elaborated upon and a clearer understanding of the intrinsic differences has been acquired Whereas Laennec s terminology defined morphological end results of pathological processes the modern terminology developed especially by the Germans conveys suggestions of their dynamics The reactions are defined on one hand as exudative and on the other as productive the former being repre ented by an exudation into the tissue spaces of inflammatory products consisting of varying mixtures of large mononuclear cells leucocytes lymphocytes erythrocytes fibrin and serum The more acute the exudative lesion the greater is the admixture of serum which accumulates particularly at the periphery of the lesion The productive lesion was so designated because of its property of adding to its own volume by the production of new cellular tissue This lesion at the start is a grey tubercle of familar cellular structure including giant cells epithelioid cells and lymphocytes it proliferates slowly as a rule and expands displacing the elements of the tissue in which it is imbedded As it grows it maintains the appearance of a conglomerate tubercle or tuberculoma with varying content of caseation granulation and fibrosis Its periphery usually is distinctly circumscribed in contrast to that of the exudative focus It is particularly important for the clinician to visualize in the living subject the predominating type of reaction in the tuberculous lesions since a judgment of their future potentialities is a large element in prognosis and the plan of treatment

There is a distinctly different trend in the evolution of these lesions determined by a variety of recognizable factors and by others which are

not so clear The same factors no doubt help to determine the original tissue reaction thus it has been well demonstrated by experimental and pathological observation that the grey tubercle is more likely to develop where the inoculum contains only a few tubercle bacilli, while an exudative reaction is favored by a large dose The structure of the involved tissue as Huebschmann Grethmann and others have observed is an influential factor the reaction being more noticeably of a tubercular morphology in compact tissues like the liver and more diffuse in loose structures like the lung Local metabolic circulatory and other poorly recognized causes seem to have a bearing on the type of reaction How these influences help to determine the later trend of the lesions is exemplified by various observations Thus the liver seldom is involved in this disease except by isolated grey tubercles extensive caseous necrotic lesions are most uncommon By contrast the lungs frequently are the seat of the latter type of destructive process Despite the obscurity which still surrounds many of these mechanisms it is important to incorporate them as well as possible into our clinical knowledge

Productive lesions when they dominate the picture often account for the mild indolent course of the disease The notable exception of course is acute generalized miliary tuberculosis in which practically all the lesions are discrete grey tubercles and this illustrates the importance of quantitative as well as qualitative differences When assaulted so abruptly at so many points the organism is overwhelmed rapidly and fatally by the toxins elaborated in thousands of tiny tubercles the local and destructive effects of the lesions play little or no part Barring such acute generalization the progressive productive lesion usually adds to its volume with a conglomeration of tubercles Central caseous necrosis may occur but usually slowly and not extensively There is a striking tendency to the formation of granulation tissue and fibrosis contributing to arrestment and sharp circumscription of the periphery With exceptions such as that mentioned the elaboration and liberation into the blood stream of toxins is not rapid Characteristically these lesions if numerically small develop and come to arrest with little or no clinical disturbance if progressive they may cause symptoms related almost exclusively to their physical structure and anatomical relationships In the brain the tuberculoma may produce the picture of an expanding tumor and this alone in the larynx the productive nodule is likely to cause only hoarseness and local irritation without soreness or pain in the epididymis the nodule may be discovered accidentally or in routine examination and not because of symptoms Growing productive tubercles like any tuberculous focus may after caseation undergo

liquefaction necrosis and ulcerate. The fibrosis about the productive focus may become very dense, leading to secondary distortions of the surrounding tissues, while the unexpelled caseous center may undergo calcareous transformation.

The exudative infiltration differs mostly in the rate and intensity of its change. These lesions by their nature are not so likely to produce the local mechanical symptoms of a tumor, although it is common to observe tensions in the tissues due to the rapid accumulation of inflammatory products. This, for instance, is the basis of the tension theory of pleural pain suggested by Bray and others, of the pressure symptoms of tuberculous meningitis and of the exquisite pain of acute tuberculous epididymitis. The exudative lesion is preeminently and almost invariably an unstable one. Usually within a short time after development it undergoes some change. This may be uninterruptedly progressive, as in the case of acute caseous pneumonia, predominantly recessive as in the case of the primary pulmonary infiltration, or variably and intermittently changing between the extremes. A progressive exudative lesion always undergoes caseation near its center and eventually, sometimes within several weeks, this is followed by colliquative necrosis and ulceration. The peripheral inflammatory reaction tends to spread and wherever new inflammatory products are exuded into the tissue spaces caseation and liquefaction may set in likewise. Necrosis affects not only the inflammatory products but also the involved anatomical structures and there are few tissues of the body which have not been found yielding to this destructive process; some are more resistant than others, and in the lung, for instance, the elastic tissue is the last to go. Secondary pyogenic infections of ulcerating lesions may modify their course. The great contrast to the swift spread and necrosis of exudative lesions is illustrated by the striking resolution of them which sometimes occurs. The serous accumulation may be absorbed rapidly and with it, at a somewhat slower pace, the cellular elements which have not undergone caseation.

In man a pronounced tendency of tuberculous lesions is to heal. Pathologically this is evidenced especially by the fibrous residue which are observed so frequently at autopsy. Pathologists, however, did not appreciate the importance and frequency of resolution until serial roentgenographic observations of the chests of living subjects were presented in recent years by clinicians. Mainly the undegenerated inflammatory products are removed by resolution and absorption. Experimentally Gardner found evidence suggesting the absorption of minute caseous foci from the lungs of guinea pigs, but there is almost universal agreement that this does not occur to any great degree either in animals or human beings.

Apparently all exudative lesions and probably the majority of productive ones which are clinically recognizable have caseous kernels which may be single or multiple The fate of these depends on their acuteness, their size and the local tissue structure and relationships In the lung a caseous focus more than one or two centimeters in diameter usually liquefies and sloughs out unless death intervenes it is most unusual to see old encapsulated foci larger than this Smaller ones after resolution of the so called perifocal inflammation has occurred and, if quiescence of the disease is maintained gradually dry out and shrink and during the lapse of many months or some years become enclosed in fibrous tissue During all this time tubercle bacilli may remain viable although it is probable that some eventually die out Undoubtedly most relapses of tuberculosis result from the exacerbation of caseous residues The question of resolution of grey tubercles has not been determined so clearly If these have not caseated it seems probable that they may be absorbed leaving behind little trace except for a small amount of fibrosis Such a mechanism may explain certain cases of interstitial pulmonary fibrosis and emphysema recognized in subjects who bear no other signs of tuberculosis The absorption of such tubercles if and when this occurs is much slower than the resolution of exudative lesions

Calcification so far as known, occurs only in the caseous parts of tuberculous lesions In a sense this is not to be regarded as a healing process but rather as evidence of the infiltration with mineral salts of necrotic foci As a matter of fact lesions which appear thoroughly calcified in the roentgenograph and which may even feel firm on palpation of the pathological specimen are often found to be chalky and partly cheesy Eventually calcified lesions, presumably after bacilli have died out may undergo ossification the bone sometimes showing marrow elements Edith M Lincoln of Bellevue Hospital has observed by serial roentgenographic study that partly calcified foci in children may undergo decalcification Sweany Wurm and others have observed that vascular granulation tissue may grow into the calcified focus perhaps accounting for certain exacerbations

The secondary mechanical structural and distortional changes resulting from the fibrosis of tuberculous lesions are familiar and I shall comment only on the changes which persist after more or less extensive resolution of pulmonary lesions It must be remembered that the resolution of tuberculous infiltrations proceeds more slowly than it does in most acute inflammations It is conceivable that serous tuberculous exudate may be absorbed from the pulmonary alveoli leaving them structurally and functionally intact As a rule however the inflam

matory process subsides so slowly that fibrous changes are produced in the interstitial tissues and in some sections of the alveoli themselves (carnification) and this may be accompanied or followed by more or less atrophy. In time secondary emphysematous changes and distortions of the bronchioles may occur. Thereafter even though the tuberculosis may be well healed the function of the involved part must be somewhat impaired. Accumulation of catarrhal exudate in the dilated and distorted air spaces is favored and this mechanism as I have described previously seems to account for the persistence of rales for many years after resolution has occurred and the patient has remained well.

The confusing term epituberculous infiltration was introduced into the literature in 1920 by Eliasberg and Neuland to designate nonspecific inflammatory reactions about tuberculous foci in the lungs of infants. In most instances the lesion has been found by pathologists to be an acute diffuse exudative tuberculous reaction as described above. In a few the picture may be explained by the development of nonspecific pneumonia distal to the point where the bronchus is obstructed by pressure of a tuberculous lymph node. Occasionally as described by Fish and Pagel the bronchus may be occluded by a caseous mass and behind this point there is a non specific inflammation. It should be remembered that tuberculous tissue is not immune to non specific inflammation.

PATHOGENESIS

Understanding of the usual way of infection of man and of the paths of progression throughout the body is based largely on the important observation that the lesions following first infection with the tubercle bacillus present certain identifying characteristics. Parrot in 1876 announced his finding of a relationship between pulmonary and lymphatic lesions which came to be known as Parrot's law (la loi de adenopathie similaires). This observation that the lesion in the regional lymph nodes almost constantly is associated with a lesion in the section of the lung which they drain was followed by further studies by Kuss in 1898 and by the publication of Ghon's work in 1916. Subsequent studies by many other pathologists such as that by Blacklock in 1932 have verified the general correctness of the earlier concepts and elaborated upon them.

The lesion at the site of the first infection has maintained the distinction of primary focus given to it by Ghon sometimes called the Ghon focus. It has been found in the lungs in more than ninety per cent of infected human subjects examined at autopsy obviously due to the fact that infection usually is by inhalation. The same mechanism seems

to account for the finding that the primary focus is seldom found at the apex of the lungs but usually in a lower lobe or lower part of an upper lobe near the pleura, presumably because particulate matter often is carried by the air currents into dependent parts of the lungs. The focus usually is single (83.53 per cent of Ghon's 170 cases), but there may be several. The size varies, as Ghon stated, from that of a hemp seed to that of a walnut, but he found most of them to be small, the majority of the size of peas. The lesion at autopsy usually is found to be well encapsulated and caseous or calcified, but most pathologists believe that the initial reaction is a small, perhaps microscopic, localized exudative lesion. Associated with it is found a lesion or group of lesions in the regional bronchopulmonary or tracheobronchial lymph nodes, and this linkage has been called the "primary complex." The section intervening between the pulmonary and the lymphatic foci usually is found to be healthy, but occasionally there is a string of lymphatic tubercles connecting the two. As a rule, the lesions in the lymph nodes are larger than that in the lung. Presumably bacilli proliferate in and escape from the lung focus very soon after the primary infection, a view which is in accord with experimental findings of Krause and Willis. The "primary complex" is a characteristic finding whatever may be the site of the original infection. In the abdomen the combination is found in the intestinal wall and the mesenteric lymph nodes; in the neck in the tonsil and cervical nodes.

The predominant tendency is for these lesions to heal. Since the primary focus in the lung usually is small and localized, it may be completely or almost completely absorbed, leaving behind only a small scar, perhaps with an overlying pleural adhesion. If, however, central caseation has occurred first, this may undergo fibrous encapsulation and within a year or two become infiltrated with calcium salts. Likewise the lesions in the bronchopulmonary lymph nodes may heal, leaving behind only calcified remnants. In the interval before healing occurs, and in the few cases in which healing does not occur, progression may take place in any one or combination of several ways, exemplified as follows: 1. The pulmonary focus may extend, caseate, liquefy, ulcerate into the bronchial system and lead to a bronchogenic dissemination. 2. The infection may spread through the lymphatics causing massive mediastinal lymphadenopathy, which in turn may go on to caseation. The enlarging nodes in children may compress the bronchi, leading to secondary nonspecific pneumonia in the lung or lobe supplied. Caseating nodes may ulcerate into the trachea or bronchus, allowing discharge of infectious pus back into the lung and causing caseous pneumonia. 3. Direct extension

from the pulmonary focus to the pleura causing an effusion is not rare These changes in infants usually are acute and rapid and the tuberculous pneumonia usually is fatal Even after a period of progression however the lesions may recede Seldom in later life the primary focus may become reactivated It is somewhat more common for such exacerbations to occur in the involved bronchopulmonary nodes even after partial or complete calcification these occasionally erode the bronchus giving rise to a foreign body effect or actually discharging infectious pus to set up new lesions in the lung

The other way of dissemination from the involved paratracheal and mediastinal nodes is by the escape of tubercle bacilli into the blood stream Organisms may enter the thoracic duct or right lymphatic duct and thence the innominate vein Having gained the venous stream they are transported through the right heart and pulmonary arteries into the lungs Here depending on the number liberated they may settle down in one or many places and a proportionate number of tubercles may develop the size of which usually is small presumably because the bacilli are implanted singly or in small clumps Just how soon bacilli may be liberated in this way seems to vary greatly but Grethmann in his pathological studies at Bellevue Hospital has found evidence of hematogenous tubercles in the lungs of infants who died in the first few weeks after birth It is probable therefore especially in infants that very early postprimary dissemination is not rare although other observations have convinced me that this likelihood decrease with advancing age Hematogenous dissemination sometimes occurs long after the primary infection particularly when the tuberculous adenitis in the mediastinum extends and the nodes become progressively caseous The dissemination may be intermittent and interrupted by periods of recession lasting for months or years

The lungs being the first organs traversed are peculiarly exposed to attack by bacilli in the venous blood stream In fact if the number is small they may all be arrested in the lungs and other organs may escape completely However in many and perhaps most cases some of the organisms complete the pulmonary circuit and enter the systemic arteries whence the place of final lodgment is quite accidental If the dose is small only a single structure such as the kidney or the spleen may be inoculated A few organisms may be destroyed at the point of lodgment otherwise tubercles sprout These may heal extend immediately or remain for varying periods as latent foci to exacerbate and progress later in life The finding of a few tubercles in the spleen kidney or other organs of persons who have died from other causes is common

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more frequently in young women an old caseous node may ulcerate through the bronchus or trachea or tuberculous lesions which have been latent in the bronchial wall for years after infection from an adjacent lymph node may break down liberating tubercle bacilli which are then aspirated to cause fresh lesions in the lung Available evidence however indicates that a much more common source exists in old pulmonary lesions usually at the apices in all probability established there during hematogenous disseminations associated with or following the development of the primary complex The reason for their persistence at the apices so called Simon foci is largely a matter of speculation A few hematogenous tubercles distributed elsewhere in the lung may it has been suggested undergo absorption more readily than those at the apex Healing of the latter doubtless accounts for most tuberculous apical scars recognized by pathologists since the days of Naegeli

However it is the tubercle which does not become cicatrized but remains caseous in its center that constitutes the dangerous focus After a dormancy varying from a short time to many years this even though minute may become reactivated especially in the altered biological conditions arising in puberty and may soften and ulcerate into an adjacent bronchiolus The liberated tubercle bacilli if not expelled may lodge in the immediate vicinity or drifting into some nearby or distant ramification of the bronchial tree may arrive at some other point in the lung where a new and larger lesion is likely to develop In these or a series of similar steps many gross bronchogenic lesions find their origin each with the potentiality of undergoing caseation and excavation

A similar succession of events may also account for the inception of progressive tuberculosis when renewed infection is acquired by inhalation from outside sources the old pulmonary foci remaining dormant and healed In fact some believe that this is the common origin of chronic pulmonary tuberculosis evidence having been adduced by Opie Aschoff and others However the weight of opinion of most recent workers such as Wurm Grethmann and Sweany is in favor of the reactivation of preexisting latent lesions Redeker has suggested that renewed inhalation of tubercle bacilli if they do not actually create new lesions may liberate into the tissues sufficient tuberculin to relight old latent foci but this is wholly speculative

Unusual channels through which the lungs may become involved in progressive tuberculosis include the rupture into the lung of a tuberculous pleural effusion or empyema which may have been encapsulated for many years and the establishment of a fistulous tract from a vertebral caries or some other adjacent osseous focus

in the experience of pathologists and gives undoubted evidence that blood stream dissemination of bacilli at or after the establishment of the primary complex is rather frequent It is relatively seldom there fore that hematogenous dissemination proves fatal when it does it is most often due to the liberation of huge numbers of organisms from a caseous focus in the lymphatic system or elsewhere resulting in acute generalized miliary tuberculosis Short of this smaller doses may be liberated at one or more intervals giving rise to less rapidly progressive forms of hematogenous tuberculosis This is observed not infrequently in negroes in whom subacute hematogenous tuberculosis is characterized by the appearance of numerous foci of varying size age and phases of degeneration in many structures such as the spleen lymphatic system liver kidneys and serous membranes protracted multiform hematogenous tuberculosis Grethmann More chronic forms apparently explainable by a smaller seeding of bacilli and greater resistance of the host are represented by the finding of healed lesions in the various structures and by the tendency of these to exacerbate at intervals after long period of quiescence Thus it has become clear that many latent lesions tardily flaring into activity in the lungs and at points remote from the lungs such as the genitalia and the bones and joints date back to hematogenous disseminations in childhood Exacerbation then may lead to local ex tension depending on the structure and the anatomical relationships of the involved part The ulcerating lesion in the kidney may be followed by tuberculous cystitis while a similar lesion in the salpinx may be followed by tuberculous peritonitis

Pathogenesis of Pulmonary Tuberculosis — Tuberculosis of the lungs and its direct or indirect consequences are by far the most important elements in progressive disease The trend of events starting most often in adolescence and early adult life is discussed with clinical correlations later since this is of such great importance in practice The lesion which most often appears as the initial step in progressive pulmonary tubercu losis is the so called early infiltration which is often especially in young people of a localized exudative character but also may be represented by a chronic conglomerate granulomatous tubercle

Its origin has been investigated by many without arriving at com plete agreement While an old primary lung focus Ghon focus acquired in childhood occasionally may break down and spread in adult life gen erally this is observed to be very infrequent Investigations in recent years suggest that lesions in the bronchopulmonary or tracheobronchial lymph nodes which may have been part of the primary complex ac quired in childhood are implicated more often Occasionally apparently

more frequently in young women an old caseous node may ulcerate through the bronchus or trachea or tuberculous lesions which have been latent in the bronchial wall for years after infection from an adjacent lymph node may break down liberating tubercle bacilli which are then aspirated to cause fresh lesions in the lung Available evidence however indicates that a much more common source exists in old pulmonary lesions usually at the apices in all probability established there during hematogenous disseminations associated with or following the development of the primary complex The reason for their persistence at the apices so called Simon foci is largely a matter of speculation A few hematogenous tubercles distributed elsewhere in the lung may it has been suggested undergo absorption more readily than those at the apex Healing of the latter doubtless accounts for most tuberculous apical scars recognized by pathologists since the days of Naegeli

However it is the tubercle which does not become cicatrized but remains caseous in its center that constitutes the dangerous focus After a dormancy varying from a short time to many years this even though minute may become reactivated especially in the altered biological conditions arising in puberty and may soften and ulcerate into an adjacent bronchiolus The liberated tubercle bacilli if not expelled may lodge in the immediate vicinity or drifting into some nearby or distant ramification of the bronchial tree may arrive at some other point in the lung where a new and larger lesion is likely to develop In these or a series of similar steps many gross bronchogenic lesions find their origin each with the potentiality of undergoing caseation and excavation

A similar succession of events may also account for the inception of progressive tuberculosis when renewed infection is acquired by inhalation from outside sources the old pulmonary foci remaining dormant and healed In fact some believe that this is the common origin of chronic pulmonary tuberculosis evidence having been adduced by Opie Aschoff and others However the weight of opinion of most recent workers such as Wurm Grethmann and Sweany is in favor of the reactivation of preexisting latent lesions Redeker has suggested that renewed inhalation of tubercle bacilli if they do not actually create new lesions may liberate into the tissues sufficient tuberculin to relight old latent foci but this is wholly speculative

Unusual channels through which the lungs may become involved in progressive tuberculosis include the rupture into the lung of a tuberculous pleural effusion or empyema which may have been encapsulated for many years and the establishment of a fistulous tract from a vertebral caries or some other adjacent osseous focus

in the experience of pathologists and gives undoubted evidence that blood stream dissemination of bacilli at, or after the establishment of the primary complex is rather frequent It is relatively seldom there fore that hematogenous dissemination proves fatal when it does it is most often due to the liberation of huge numbers of organisms from a caseous focus in the lymphatic system or elsewhere resulting in acute generalized miliary tuberculosis Short of this, smaller doses may be liberated at one or more intervals giving rise to less rapidly progressive forms of hematogenous tuberculosis This is observed not infrequently in negroes in whom subacute hematogenous tuberculosis is characterized by the appearance of numerous foci of varying size age and phases of degeneration in many structures such as the spleen lymphatic system liver kidneys and serous membranes protracted multiform hematogenous tuberculosis Grethmann More chronic forms apparently explainable by a smaller seeding of bacilli and greater resistance of the host are represented by the finding of healed lesions in the various structures and by the tendency of these to exacerbate at intervals after long periods of quiescence Thus it has become clear that many latent lesions tardily flaring into activity in the lungs and at points remote from the lungs such as the genitalia and the bones and joints date back to hematogenous disseminations in childhood Exacerbation then may lead to local ex tension depending on the structure and the anatomical relationships of the involved part The ulcerating lesion in the kidney may be followed by tuberculous cystitis while a similar lesion in the salpinx may be followed by tuberculous peritonitis

Pathogenesis of Pulmonary Tuberculosis —Tuberculosis of the lungs and its direct or indirect consequences are by far the most important elements in progressive disease The trend of events starting most often in adolescence and early adult life is discussed with clinical correlations later since this is of such great importance in practice The lesion which most often appears as the initial step in progressive pulmonary tubercu losis is the so called early infiltration which is often especially in young people of a localized exudative character but also may be represented by a chronic conglomerate granulomatous tubercle

Its origin has been investigated by many without arriving at com plete agreement While an old primary lung focus Ghon focus acquired in childhood occasionally may break down and spread in adult life gen erally this is observed to be very infrequent Investigations in recent years suggest that lesions in the bronchopulmonary or tracheobronchial lymph nodes which may have been part of the primary complex ac quired in childhood are implicated more often Occasionally apparently

Diagnostic Methods in the Approach to Tuberculosis

History

The information to be obtained from careful and intelligent history taking is very great This of course must not lead to ignoring the fact that the real inception of the disease usually is not attended by symptoms of which the patient is aware To forget this would be to deny the possibility of really early diagnosis in the majority of cases and underestimate the principle that the successful conquest of the disease depends largely on its detection before symptoms have developed or become apparent In fact there is a well founded conception that the approach to diagnosis should not be primarily by way of symptoms but rather by some means of detecting lesions and then exploring further to find their significance Symptoms sufficient to bring the patient to the physician usually are those of bronchogenic tuberculosis which has gotten well beyond the early phase

One cannot emphasize too strongly therefore that diagnosis of early disease depends on the physician who is familiar with the asymptomatic or only vaguely symptomatic manifestations of the lesion History taking should be planned according to a conception of pathogenesis remembering that the interval between clinical disease and the original lesion may be long Evidence of a source and time of infection recent or remote is sought Then recalling the customary course questions are asked to ascertain whether there has been a typical sequence of symptoms It is important to learn for instance whether chronic hoarseness may have been preceded by cough expectoration and hemoptysis The chronicity long periods of arrest complications and secondary functional possibilities which are so characteristic of tuberculosis always should be borne in mind There probably is no disease in which the skillful questioning of the patient will elicit more information for a complete understanding of the existing situation and the events which may have antedated it

Physical Examination

The information to be obtained depends on the skill and the carefulness of the examiner In the first place it may be said that the physical examination should be complete and searching not only to gain an adequate idea of the patient s physical constitution but also to detect possibly widely scattered lesions constituting a systemic disease These

The location of the early infiltration or granuloma may be anywhere in the lungs usually in one lung and most frequently just below the apex There is a predilection for the posterior part of one of the upper lobes and if the lesion is in a lower lobe it appears also as a rule in the posterior and upper portion Successive bronchogenic spreads likewise may appear in any section of the lungs usually starting in the immediate vicinity of the earlier lesion here again the upper and posterior parts are favored one suggestion being that this is on account of the habitual recumbent posture during sleep when bronchial discharges are more likely to accumulate and be aspirated The influence of the physical character of the bronchial discharges whether profuse and fluid or scanty and viscid in determining the distribution extent and character of secondary lesions is important and is discussed further Grethmann has stressed also the influence of the concentration of tubercle bacilli and tuberculous toxins in these discharges

Progressive disease leads to complications the most frequent of which is invasion of the pleura by direct or lymphatic extension Surface contamination leading to infection of communicating canals is common Tubercles exudative infiltrations ulcers, granulomas and scars may arise by this mechanism in the bronchi larynx and lower intestine Other structures less often involved include the mouth tongue middle ear and pharynx The infrequency of severe hematogenous disseminations after the establishment of progressive pulmonary tuberculosis is a striking distinction from the consequences of primary infection in infants and young children This suggested the conception that in adults tuberculosis usually is a chronic organic lesion (lung kidney etc) and that extensions are most often through the preformed communicating canals (intra canalicular)

In the pathological sense the arrest of pulmonary tuberculosis is indicated by complete fibrous encapsulation of caseous foci remaining after the processes of sloughing and resolution have been completed The competency of the fibrous capsule as a rule increases with age so that eventually the focus may be sharply and permanently isolated from surrounding alveoli It is from these foci if the capsule is not competent that exacerbations occur later with a repetition of the steps of liquefaction necrosis ulceration and bronchogenic extension There is undoubtedly a direct correlation between the size of the encapsulated caseous focus and the liability to later relapse A large focus is most dangerous a small one less so a tuberculous ulcer which has healed after sloughing out its caseous content still less and a tubercle which cicatrizes without caseation least

X ray Examination

The x ray has come to occupy such a dominant position in the diagnosis of pulmonary tuberculosis that it is considered indispensable For the detection of many early lesions it is the only diagnostic means and for determination of the extent distribution and character of early as well as advanced lesions it is a necessary part of the examination often revealing features which are undiscoverable by classical physical methods However to say that the x ray should supplant physical examination is quite unreasonable since the latter may reveal phenomena entirely unsuspected by roentgenography alone To obtain the maximum information from x ray examination one must appreciate some of the elements of technique and become familiar with criteria of interpretation If the clinician is able to interpret the shadows he may correlate these findings better with other features of the clinical picture

Fluoroscopy is of value in the diagnosis particularly since it permits study of the movements of the thorax and its contents and views of the densities from various angles The intensity of the fluoroscopic image is somewhat limited by the relatively low penetrability of the x rays employed and lesions of small extent and light density may be overlooked particularly where the densities of thoracic structures such as the ribs the heavy muscles over the apex of the lung and the large blood vessels at the hilum obscure the field The percentage of error will vary with the skill and carefulness of the examiner at least 10 to 15 per cent of small tuberculous lesions will be missed Fluoroscopic examination is invaluable in helping to localize thoracic lesions such as pleural effusion cavities and adhesions In the practice of artificial pneumothorax the method is a most useful control of the mechanical effects of the treatment In this connection it should be stated that some patients from frequent fluoroscopic examinations develop an erythema of the skin with later slight atrophic changes This is shown most often by a reddish brown pigmentation in the interscapular areas where the ray frequently is concentrated The safe dose should not be exceeded Some observers have even suggested that too frequent fluoroscopy may aggravate tuberculous lesions

The roentgenograph is the most efficient means of recording the shadows of pulmonary lesions The usual photographic medium is the double coated cellulose acetate film Sensitized paper in single sheets or in rolls has found favor with some particularly in case finding among large groups of people While it is efficient for such purposes and is somewhat superior to fluoroscopy the paper photograph does not afford

changes may be slight such as an infiltration of one vocal cord a phlyc tenule in the conjunctiva a swollen and buried lymph node a localized skin rash or a nodule in the epididymis Examination of the thorax like wise should be systematic and thorough It is hardly necessary at this time to emphasize the necessity of having the chest laid bare in order to examine it adequately The classical procedures of inspection palpation percussion and auscultation all have their value but one of the most important is the proper technique to elicit rales In advanced cases these may be heard on quiet breathing but ordinarily only after the cough In order to secure the proper cooperation of the patient it is of value to illustrate carefully just what is meant and the physician may go through the procedure breathing out quietly but fully giving a short cough at the end of the expiratory effort and then breathing in quickly Occasionally it is possible to elicit rales only after a series of three or four sharp successive coughs without intervening inspirations This maneuver results in a maximum expulsion of air from the bronchioli and alveoli and a sudden reinflation during the succeeding sharp inspira tion It is just at the end of the expiratory cough or the beginning of the following inspiration that rales are most likely to be heard The smooth ness with which the patient goes through this movement may determine whether the physician elicits this most important sign differences in the observations of different examiners are due more often to the technique employed than to variations in the lesions Meticulous auscultation of the whole chest with this technique is necessary since a limited lesion may produce rales only in a small section

The limitations of examination of the thorax must always be appre ciated since this procedure alone frequently does not give an adequate idea of the full extent of the lesions Extensive infiltrations may give so few signs as to be largely unappreciated especially in children be cause of their inability to cooperate in the examination The scarcity of abnormal signs is more characteristic of light disseminated lesions as in hematogenous tuberculosis than it is in localized concentrated ones Fibroid thick walled cavities usually are detected with ease while large thin walled ones surrounded by fairly healthy parenchyma fre quently are missed If very moist bubbling or consonating rales are included as suggestive of cavity the error is less common The unre liability of physical examinations to detect the early infiltration is no torious By contrast râles may be much more extensive than would be suspected from the roentgenographic picture in which case they often are caused by the secondary effects of a tuberculous infiltration which has undergone resolution and fibrosis

shadows in this region are frequent Small inflamed or caseous lymph nodes in the hilum regions or in the mediastinum cannot be detected by the x ray

Finally it bears repeating that x ray methods are of maximum value only if correlated closely with other findings The shadows are not specific and alone may be very deceptive Experience and judgment however will permit the development of diagnostic accuracy which cannot be attained without the use of this important method

Examination of the Sputum

This is the final confirmatory test in the diagnosis of tuberculosis though under many conditions it is not possible to obtain this evidence Meticulous care should be used starting with the collection of the specimen Many tuberculous patients report that they do not raise any discharge from the throat This may be true as judged by the failure of other studies to reveal any evidence of ulceration or excavation in the lungs Often enough however it is not so since the patient unconsciously may swallow the discharge as it slowly moves into the pharynx This is rather uniformly true of young children frequently of girls and women but less so of men who as a class habitually spit The patient is carefully instructed to expectorate into a container any material which rises into the throat particularly in the morning This may be evidenced only by the clearing of the throat and not necessarily by cough In the cases in which instruction does not produce results or in young children recourse must be had to the collection of laryngeal pharyngeal or gastric specimens In children laryngeal or pharyngeal swabbing may by stimulating gagging bring away some mucopurulent material and particles sometimes have been obtained by holding a laryngeal mirror over the glottis and asking the patient to cough If gastric lavage is necessary this is carried out in the morning before breakfast After a sterile stomach tube is inserted four to eight ounces of clean preferably freshly distilled water is introduced and immediately aspirated into a clean container The centrifugated sediment from this collection may then be examined It has been said at times that bloody sputum or the blood from hemoptysis is not suitable for laboratory examination but this is completely erroneous and it may in fact be precisely the specimen which is most likely to show tubercle bacilli

It is important to collect the daily output of sputum in a container preferably transparent so that variations in the quantity and character may be judged The character is determined according to the color and

a range of density and contrast equal to the celluloid negative The difference frequently is minimized by improvements of technique Recently a method has been devised to photograph the fluoroscopic image of the chest on a miniature negative which after development is visualized by projection on a screen This would seem to be economic but its usefulness and efficiency remains to be determined

Proper radiographic technique is most important The standard view is the postero anterior (patient facing the film) The patient takes a deep breath in order to allow maximum illumination of the lungs the important point being that pulmonary detail is visible because of the contrast created between anatomical structure and surrounding air spaces These principles have to be compromised of course in the case of an infant or young child In order to minimize distortion from diverging rays it is desirable to place the film at least four feet from the anode of the x ray tube and five to six feet is preferred if possible Rapid exposure (one tenth second or less) is desirable in order to minimize the blurring effects of moving parts chiefly the heart and pulmonary vessels Stereoscopic views and various oblique lateral and anteroposterior views with the patient standing leaning or reclining in specially selected positions yield much information for accurate diagnosis and localization The oblique view is invaluable for the detection of certain lesions which lie in the mediastinum or are obscured by other structures in the standard view Recently the technique of laminagraphy (tomography stratigraphy planigraphy) has been developed to permit the visualization of selected planes of the thorax While there is considerable blurring which prevents recognizing fine details the method has been found useful to portray pulmonary cavities and other changes which with the ordinary technique are completely obscured by overlying densities Other techniques which are more or less sufficient for such purposes include the use of deeply penetrating x rays sometimes with the laminated grid and sometimes after the injection of contrast substances like iodized oil

The limitations of the roentgenograph must be recognized even though the proper use of this method is of utmost value Depending on the density of overlying structures soft tuberculous lesions of a centimeter or so in diameter may be easily obscured while isolated small tubercles often cannot be distinguished from the density of certain normal structures In the hilar regions particularly the possibility of error in interpretation is great Tuberculous lymph nodes here can be identified only if they are so large as to protrude beyond the normal hilar densities or if they have undergone sufficient calcification to cast shadows quite distinct from surrounding densities Mistaken interpretations of vascular

slants with two loopful of material or ten slants with four loopfuls equals inoculation of one guinea pig in positive results; others use fewer tubes. The general experience is that as many as 50 per cent of specimens which are negative on simpler examination will be found positive for tubercle bacilli by animal inoculation or culture. Pinner, Woolley, Willis, Bogen and others have found that more than 98 per cent of patients with active pulmonary tuberculosis have tubercle bacilli in the sputum. The importance of an exhaustive search in diagnosis and differential diagnosis therefore is apparent.

Examination of Other Material for Tubercle Bacilli

Frequently the only material to be obtained for bacteriological examination is some excretion, discharge or exudate other than sputum, such as pleural exudate or urine. Similar principles apply in these examinations also. In the case of serous fluid from the pleura, tubercle bacilli frequently cannot be demonstrated by direct microscopic examination, and it is necessary to precipitate the protein in the exudate, collect the sediment and treat this by culture or animal inoculation. Since bacilli may be scarce in such exudate the likelihood of finding them is less if only 10 to 20 c.c. are treated or used for inoculation; it is better to treat as large a quantity as may be obtained by thoracentesis. Purulent discharges from tuberculous sinuses may have to be digested with sodium hydroxide solution before inoculation or culture. Occasionally it may be desirable to search the feces for tubercle bacilli, in which case special procedures have to be carried out for this purpose.

Occasionally in the sputum or other specimens acidfast organisms are discovered and are found to be non-pathogenic or rarely belonging to other species, such as the actinomyces. The smegma bacillus has to be eliminated when the specimen is urine, particularly in the case of a female; paratubercle bacilli possibly may be present in gastric washings or in the wax of the ear canal, and acidfast saprophytes have been reported in non-tuberculous pulmonary suppurations. These forms seldom have to be considered in clinical practice, and if necessary, the distinction can be made by culture and animal inoculation of the isolated organism.

Examination of the Blood

Except for the occasional successful cultivation of tubercle bacilli from the blood there is no test of this element which is specifically diagnostic of significant tuberculosis. Numerous tests have been devised, both sero

consistency, whether mucoid mucopurulent or fluid The odor also should be noted carefully since this is important in diagnosis Mixtures of blood may be present and if free hemorrhage occurs the amount of blood should be estimated

Laboratory examination is of particular importance since the likelihood of finding tubercle bacilli varies greatly according to the technique employed The microscopic identification of the bacillus depends on its capacity to resist acid decolorization acidfastness the standard staining method being the Ziehl Neelsen or some modification of it

In brief the following results are obtained by standard laboratory examination of the sputum (a) Careful examination of selected mucopurulent particles smeared directly on the glass slide and stained reveals acidfast bacilli in the majority of cases in which there is a pulmonary tuberculous cavity especially if this is of recent development This method fails in 20 per cent or more of the average run of cases particularly if the discharges are small and the pulmonary process is of a chronic character also if bacilli are greatly diluted by the admixture of blood mucus or saliva

(b) If single smears fail to show tubercle bacilli 30 to 40 c c of sputum should be collected over a period of three or four days or more if necessary in a clean container This may be digested and liquefied by mixture with sodium carbonate (1 per cent aqueous solution) or sodium hydroxide (3 per cent aqueous solution) the mixture then being allowed to stand in the incubator at 37 5° C over night The liquefied solution then is centrifugated and the sediment collected on a slide and stained According to the material and care employed 20 to 30 per cent of the tuberculous cases found to be negative on examination of the smear alone now will show tubercle bacilli Other methods of concentration have been suggested such as the flotation method and have been found to be quite efficient

(c) Even concentration and sedimentation of specimens may fail to produce positive results if the tubercle bacilli are scanty Woolley has found that at least five thousand bacilli must be present in each c c of material before they can be detected readily on microscopic examination Others have placed a higher minimum The search cannot be said to be complete therefore until the sputum properly treated has been subjected to culture or guinea pig inoculation Such inoculation, while not absolutely infallible rarely fails to divulge the presence of organisms since the guinea pig almost invariably develops tuberculosis if they are present The relative merits of cultural methods depend on the skill and technique employed but Woolley found that inoculation of twenty culture

slants with two loopfuls of material or ten slants with four loopfuls equals inoculation of one guinea pig in positive results others use fewer tubes The general experience is that as many as 50 per cent of specimens which are negative on simpler examination will be found positive for tubercle bacilli by animal inoculation or culture Pinner Woolley Willis Bogen and others have found that more than 98 per cent of patients with active pulmonary tuberculosis have tubercle bacilli in the sputum The importance of an exhaustive search in diagnosis and differential diagnosis therefore is apparent

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logical and cytological and these in the hands of experienced technicians and clinicians may be of considerable value in judging the activity of the lesions Many years ago Webb and others found that the relative increase of the lymphocytes of the blood accompanied clinical improvement and since then numerous studies of the cytological blood picture have been made, particularly in late years by Medlar and by Sabin Smithburn and others In the judgment of Medlar increase in the leucocytes and the polymorphonuclear neutrophil elements is significant of abscess formation while a rise in monocytes may be indicative of new tubercle formation and a rise in lymphocytes of active healing processes

Smithburn Sabin and Hummel found from a study of tuberculosis in rabbits that the monocyte lymphocyte ratio is a more sensitive indicator of tuberculous infection than any of the blood cells alone or the neutrophil lymphocyte ratio Of the individual cells they found the monocyte most sensitive in that it was the first to show significant change but the lymphocyte was the more reliable for prognosis as the degree of decline was roughly proportional to the severity of the infection There can be no doubt that such cytological shifts go hand in hand with and sometimes yield the first evidence of certain local changes in the lesions To be of greatest value the cells should be studied at intervals of weeks or months so as to show any changing trend Technique skill and care is most important since otherwise the error may be significant and confusing Except by inference it can scarcely be expected that the cytological picture will reveal the immediate or ultimate prognosis but only the current trend This together with clinical and other findings to complete the picture may make a prognosis more accurate The Schilling count has been helpful to some but I have not learned to depend on it

Estimation of the erythrocyte sedimentation rate is being used widely for similar purposes Varying degrees of acceleration may be found in active and advancing tuberculosis and often this is a more sensitive indicator of the toxemia than symptoms like fever and tachycardia Sometimes also an accelerated rate may well arouse the suspicion of activity in a lesion which has not yet been revealed by other findings In many early cases and even in many chronic fibroid cavernous cases the sedimentation rate is found well within normal limits Such negative findings therefore do not give assurance that the tuberculosis is not active or menacing Among other tests which show deviations in the tuberculous patient are the complement fixation test serum coagulation test of Weltmann and the Vernes resorcin test These have not been found to yield as much information to the clinician as the erythrocyte sedimentation rate and the cytological picture Numerous other changes have been

observed to occur in the course of tuberculosis in the various constituents of the blood (mineral salts proteins vitamins etc) but these if profound usually are demonstrated in advanced or terminal cases and have not been found to be of practical diagnostic value

The sensible attitude for the clinician is to appreciate these tests for their part in the whole picture which may vary from an insignificant one to a dominant one It is his function to evaluate each datum and give it its proper place Certainly no one should rely exclusively on any single laboratory test to answer finally the question of activity or immediate prognosis much less the ultimate prognosis

The Tuberculin Test

Since the original manufacture of tuberculin by Koch the effects of the injection of this material have intrigued clinicians and the demonstration by von Pirquet of a local reaction upon its application to the skin has been followed by its wide use in diagnosis Numerous methods have been employed including the percutaneous (Moro test) subcutaneous cutaneous (Pirquet) and intradermal (Mantoux) Recently a patch test has been proposed by Vollmer Some of these have the advantage of simplicity and ease of application but the intracutaneous test is considered generally to be the most accurate and reliable The Pirquet test and the patch test have been found to approximate in accuracy the intracutaneous test with 0 01 mgm old tuberculin (O T) (Court) For the Pirquet test a drop of undiluted old tuberculin is applied to a small point of the flexor surface of the forearm and through this the skin is lightly scarified by a needle or borer A nearby control using salt solution may be used but is hardly necessary

The Mantoux test is performed by using a tuberculin syringe and fine (26 gauge) needle injecting 0 1 c c of a given dilution of old tuberculin into the layers of skin to create a whitish wheal If old tuberculin is used this is diluted so that the injected dose contains 01 0 1 or 1 0 mgm of the substance as desired Because of the fact that old tuberculin from different manufactures was found to vary considerably in its potency the Medical Research Committee of the National Tuberculosis Association undertook to encourage the development of a standard substance This has resulted in the production by Long and Siebert of a purified protein derivative (P P D) which contains a constant and uniformly active amount of the pure protein The site of injection is observed at the end of twenty four forty eight and seventy two hours a positive reaction being represented by an area of slight swelling which is visible and pal

pable in the skin and which is accompanied by redness later brownness and desquamation The intensity of the reaction varies and if slight is regarded as + if intense as ++++

Very intense reactions with any method of testing may result in vesical formation and possible ulceration Occasionally the patient may have a constitutional reaction evidenced by malaise and fever during the subsequent twelve to forty eight hours and in a few cases a lymphangitic reddening may be noticed along the arm and the axillary lymph nodes may be swollen The dose of tuberculin therefore must be regulated carefully If P P D is used the dose may be calculated in terms of O T Harmful reactions about the existing lesions must be guarded against since heavy overdosage may cause an acute perifocal inflammation and occasionally has been seen to result in softening and breaking down of the focus When questionable lesions are identified therefore it is desirable to start testing with minute doses of tuberculin (0 001 mgm old tuberculin or 0 000002 mgm P P D) If there is no reaction to this a dose of 0 01 mgm old tuberculin or 0 00002 mgm P P D may be employed after four or five days Once a reaction is elicited it is unnecessary and undesirable to repeat the test

Case Finding Methods

Since tuberculosis has become more and more a public health problem and the control of the disease has been placed more in the hands of public agencies the importance of discovering the disease among members of the community has received greater recognition On one hand public health officials have accepted this as one of their proper functions and on the other the search for cases has been stimulated by the failure of other time honored methods to uncover the disease before it has entered the advanced stages in a large proportion of the cases Application of direct case finding methods involves education of the public the tuberculin testing of large groups of people and x ray examination of the chests of apparently healthy members of the population The usefulness of such schemes in diagnosis will be discussed later

Variable Phases of Tuberculosis

Numerous attempts have been made to codify the knowledge of tuberculosis into systems which would be useful clinically and at the same time sound pathologically Systems vaunted for their completeness commonly have had the disadvantage of excessive intricacy while some

with the virtue of simplicity have suffered from inadequacy. Indeed too severe an attempt at codification defeats its own purpose which is a comprehension of the whole picture with all its perceptible and imperceptible gradations. Tuberculosis is not like an edifice constructed according to architectural design and therefore easily separable into its components and so classified, rather like a natural landscape which may be explored in its various areas but to be understood and appreciated must be contemplated as one.

On a pathogenetic basis there is much to be said for classifying the disease as some have preferred according to the phases of primary infection, lympho hematogenous dissemination and chronic organic phthisis or even into primary infection and reinfection types between which allergy is proposed as one line of distinction. But the attempts are often hampered by the necessity of striking a line of cleavage where the separation is not clear cut and natural. The difficulty is illustrated by differences at least in degree between the immediate results of primary infection in infants and in adults.

Primary Infection in Adults

It is becoming evident that more and more people arrive at adult life *before they first acquire the infection*. This is particularly true in certain sections like the rural middle west of the United States. Sweany has reported pathological observations of lesions from primary infection in adults and notes a difference from the characteristic lesions in children. He finds a predominating tendency of the primary lesion to remain confined in the pulmonary parenchyma with little or no involvement of the regional lymph nodes. The parenchymal lesion according to him may not have the same stability as a comparable one due to obvious reinfection. During the past ten years I have been particularly interested in this question and have observed the cases of about five hundred young nurses who entered the training school of Bellevue Hospital insensitive to the tuberculin test (1.0 mgm O T intracutaneously). With few exceptions they all reacted to the test later in their course of training. Pulmonary lesions have developed in this group a little more often than in those who entered tuberculin positive. In no case among those becoming tuberculin positive for the first time have my associates and I observed definite enlargement of the bronchopulmonary lymph nodes, in other words we have never been able to identify the characteristic primary complex but only the lesion in the pulmonary parenchyma. With one exception no hematogenous lesions have been observed and there

have been no deaths among this group. While newly developed tuberculin sensitiveness as demonstrated by various observers (Opie and MacPhedran, Lumsden, Long) does not necessarily prove that tuberculous infection has never before occurred, nevertheless it is the only available means of identifying the group among which this is the case. There seems to be no doubt that in the human being age alone, at least up to a certain point, brings with it an increasing natural resistance against tuberculous invasion, and that pulmonary lesions developing in adults act very much the same whether due to primary infection or to reinfection. Also the likelihood of secondary lesions developing from hematogenous disseminations seems to be decidedly less than it is when primary infection is acquired in infancy. This example shows the unwisdom of attempting to ascribe constant and fixed implications to individual factors in tuberculosis and especially to employ these as a basis of rigid classification. While the threads of pathogenetic continuity often can be traced, they run very deviously. Consequently it is fruitless to seek for patterns into which individual cases may always be fitted. In the following paragraphs this truth is not forgotten. I discuss prevailing trends separately for convenience, knowing that Nature does not preserve such separations at all times.

Tuberculosis in Children

Tuberculosis in children, while essentially identical with that in adults, presents certain aspects in diagnosis, prognosis and management which warrant separate consideration.

First Clinical Manifestations

While the first infection in children usually is respiratory and the first lesions appear in the lung, it must be emphasized that the predominant ones develop most often in the bronchopulmonary and mediastinal lymph nodes. This is one reason why strictly pulmonary symptoms are not a prominent feature. When the infection extends, usually it is through the lymphatics and blood stream at first, not often by ulceration into and through adjacent tissues.

The first clinical developments, therefore, frequently are represented by constitutional symptoms of toxemia and possibly by the outcropping of tubercles in visible structures. Complete absence of clinical manifestations is common. The lesions may be identified by x-ray examination of the chest in probably less than 20 per cent. of the infected, and in only

a minority of these will symptoms assert themselves or become so striking as to bring the patient to the physician. As a rule the time of the first infection is unknown to the parents or the physician.

Symptoms, if any, are not likely to appear until some weeks or months after the lesions have been established. Then the child may have mild constitutional disturbances such as slight irritability, restlessness, mild digestive disturbances, loss of weight or failure to register the usual progressive gain. In a few cases a rise in temperature, which has been called the "primary fever," may be observed by recording the curve three to four times or oftener daily. This, as a rule, rises slowly to 101° F. or 102° F. and then slowly recedes, the whole episode occupying a period of two to four weeks. Such vague symptoms may well arouse suspicion, particularly when it is known that the child has been exposed to a patient with open pulmonary tuberculosis.

History of Contact

It is possible to identify the source of infection in infants and young children more often than in older people because of the limited circle of contact. When the child presents suggestive or definite symptoms, search for such a source case, especially in the household, is indicated always. Likewise, when such exposure is known to have occurred, the children of the household should be tested periodically with tuberculin to detect the possible development of signs of infection.

Early Manifestations

Aside from vague constitutional disturbances, careful inquiry and examination may reveal findings related to early hematogenous dissemination or to some peculiar evidence of the toxemia. Erythema nodosum has been observed as a rather early manifestation in these children, particularly by Wallgren, Heimbeck and other Scandinavian clinicians. In the United States this is uncommon, and the difference remains to be explained. Erythema nodosum is not a specific lesion, since it occurs also in the course of other infections, such as rheumatic fever. Its discovery in the child should at least lead to further investigation for tuberculous infection.

In a small minority of children isolated hematogenous lesions may give the first clue, such as phlyctenules in the conjunctiva or papulonecrotic tuberculides in the skin. In a few instances, especially in infants, early dissemination of the infection is not detected until serious hematoge

nous invasions manifest themselves in the form of tuberculous meningitis or generalized miliary tuberculosis

Later Manifestations

The great variation of the later manifestations of progressive tuberculosis in children is due largely to chance which determines whether the paths of extension will be in one direction or another The tendency toward lympho hematogenous dissemination with fatal termination in infants becomes relatively less prominent in older children in whom the progressive changes usually are more localized less intense and less acute and localizing symptoms are more common Swelling of the lymph nodes is not uncommon and this may occur anywhere in the lymphatic system Enlargement of superficial nodes such as the cervicals auriculars axillaries and inguinals may become promptly manifest (see Tuberculosis of the Lymph Nodes) Inflammation and caseation of abdominal nodes may cause vague pains and digestive disturbances the nature of which is not easily identified Early and progressive involvement of the genitourinary tract is observed in a few cases and in addition to the general symptoms of the toxemia may give rise to urinary frequency hematuria and pyuria

When as in most cases such manifestations are not apparent the symptoms are related mainly to developments in the thorax and these vary greatly The cough may be of several types If the lesions in the lungs or in the lymph nodes ulcerate into bronchi or the trachea a rather loose moist cough develops which is most pronounced in the early waking hours and is productive of mucopurulent discharges which usually are swallowed In other cases the cough is spasmodic hard dry rasping and sometimes stridulous and brassy due to the compression and irritation of the trachea and bronchi by greatly enlarged adjacent lymph nodes this is observed more often in the very young in whom the bronchi are narrower and more yielding During the spasm the neck veins may stand out and the face become congested and livid In some cases partial relief is afforded when the child sits up Likewise the character of the breathing may be significant Quick breathing may be explained entirely on the basis of toxemia but in infants sometimes it is due to mechanical pressure of lymph nodes definite stridor usually expiratory may develop with inspiratory depression of the lower intercostal spaces and of the suprasternal soft tissues The embarrassment may be interpreted by the parent as asthma or croup and in severe cases the respirations may have a wheezing quality simulating true asthma Hemoptysis may occur but

is most unusual in children the apparent reason being that they do not often develop large and chronic pulmonary cavities However continued invasion of the lungs leads to manifestations much like those observed in adults If excavation occurs the cough is chronic and complicating lesions may develop in the intestine or the larynx Wasting continues until the child becomes emaciated and dies possibly with some intervening hematogenous dissemination of the infection

Pleurisy with effusion by no means is rare in children giving rise to fever which may amount to 104 F to 105 F possibly leading to dyspnea from mechanical displacement of the mediastium and running a course of six to eight weeks after which the exudate may be absorbed slowly The involvement of several serous cavities simultaneously occurs more often than it does in the course of chronic tuberculosis in adults

The subsequent development of cases in which the lesions are subacute or chronic is most protean The first recognized lesions may subside and tend to heal and the child for some months or years may have a relatively healthy period only to break down later with reactivation of the same lesion and extension to other parts by various paths of dissemination

Diagnosis after Detection of Clinical Manifestations

Clinical symptoms indicate first a thorough physical and x ray examination The finding of changes by physical examination alone usually means that the lesions have become large and extensive unless they are quite superficial as in the skin Abnormal areas of dullness may be detected in the chest there may be definite alterations of breath and voice sounds and râles may be heard but such findings are relatively infrequent Attention is directed particularly to the mediastinum because of the well known tendency of the lymph nodes there to be affected Unless the involvement is rather massive however the physical examination usually is quite negative Outspoken findings such as paravertebral or parasternal dullness the D Espine sign and the tracheal whisper beyond normal limits are indicative of lymphadenopathies widely filling the mediastinum

Chief reliance therefore is placed in the *roentgenograph* the superiority of which for this purpose *is even more striking than in adults* Since children so often present lesions referable to primary infection the question naturally arises whether the roentgenograph will reveal findings identifying them as such There is no single density pathognomic of primary infection but the primary focus usually is portrayed in the lower

part of one pulmonary field by a localized and more or less rounded shadow which may be soft and light or dense and compact Widening of or calcification in the hilar shadow is taken to represent the diseased bronchopulmonary nodes in the other pole of the primary complex Deviation from these appearances however is frequent The pulmonary densities may appear as soft diffuse more or less homogeneous or mottled clouding in limited or large sections Fine studding stippling and nodulation scattered more or less uniformly in both lung fields particularly in upper parts, is suggestive of tubercles implanted through infection by way of the blood stream Excavations when they occur are represented by small honeycombed or larger rounded rarefied areas in the midst of the mottling or clouding The widening of one hilar density may be the only suggestion of lymphatic invasion but sometimes the mediastinal border above this is displaced outward the widening appearing as a uniform density with a straight or a scalloped border Mediastinal and hilar widening may be apparent on both sides The densities of pleuritic changes are sometimes observed as thickening of an interlobar fissure a tenting of the diaphragm silhouette or by more or less clouding from an effusion which is seen first in the costophrenic sinus Not infrequently the parenchymal lesion is very small or even indiscernible and the widening of the hilar densities and of the mediastinum may be the only detectable change It is to be repeated that small pulmonary lesions and caseous lesions in the bronchopulmonary and mediastinal lymph nodes not causing gross enlargement may be invisible in the roentgenograph even though these are progressive and may give rise to fatal dissemination Some may become visible later when they are infiltrated with calcium salts but this seldom occurs until after the lapse of two years or more The finding of such roentgenographic changes in a child with any of the symptoms or manifestations mentioned above warrants a presumptive diagnosis of tuberculosis which is almost assured if a bronchopulmonary or mediastinal lymphadenopathy is demonstrated and certainly if secondary lesions such as tuberculides of the skin are found

Confirmation of the diagnosis if necessary rests on further investigation and observation The importance of the history of contact with an open case of pulmonary tuberculosis has been mentioned and the discovery of a contaminated milk supply in countries where bovine infection is prevalent may be significant The place of the *tuberculin test* in diagnosis in the case of the sick child deserves special consideration It should be performed always but with due attention to the possibility of harm This can be avoided by employing a small dose of tuberculin at the start (0 001 mgm of old tuberculin or 0 000002 mgm of P P D

intradermally) and increasing in steps of ten times the preceding dose at intervals of four or five days until a positive reaction is noticed It is unwise to inject more than 1 0 mgm of O T or its equivalent in P P D into the skin of a sick child With very few exceptions the tuberculous child reacts to a small dose In the terminal phase of the disease even large doses may not elicit a reaction but usually it is unnecessary to try these Therefore the failure of a sick child who harbors demonstrable pulmonary lesions to react to 0 1 mgm of O T weighs strongly against the diagnosis of tuberculosis A reaction establishes the fact of infection and this may make the diagnosis almost conclusive but it is not direct evidence that the known lesions are tuberculous With few exceptions this will be demonstrated by further observation

In cases of active thoracic disease in children frequently it is possible to discover tubercle bacilli in discharges obtained by the pharyngeal swab or in the gastric washings and this attempt should not be omitted since a positive finding finally settles the question Otherwise clinical observation as a rule brings one to an accurate conclusion Persistence of the characteristically coupled pulmonary and lymphatic roentgenographic shadows with or without the persistence of symptoms progressive or slowly retrogressive changes in the lesions during a period of a few weeks to several months makes the diagnosis of tuberculosis practically sure even though tubercle bacilli may not be discovered Bacilli are demonstrated less often when the lesions are confined almost exclusively to the lymph nodes in which case the positive contact history the positive tuberculin test and persistence of or slow change in the lymphadenopathy warrants a diagnosis of tuberculosis unless there is proof of some other cause

Differential diagnosis in cases in which there is little or no demonstrable lymphadenopathy and the lesions are confined to the pulmonary parenchyma takes into consideration most often the various pneumonias especially simple bronchopneumonia and suppurative pneumonia also bronchiectasis If the predominating lesions are in the bronchopulmonary and mediastinal lymph nodes Hodgkins disease and rare tumors may have to be ruled out The means of differentiation are in principle the same as in adults and are discussed later Observations during a few months may be necessary to settle the diagnosis in the unusual case

Diagnosis of Symptomless Tuberculosis in Children

The early lesions in children are seldom revealed because of symptoms of illness Identification therefore must rest on other leads The fact is that most of these infections are unknown until routine tuberculin tests

are carried out This is particularly desirable in the case of any child who comes from a tuberculous family or who has had any possible exposure Those who react should have a roentgenograph of the chest since the physical examination is almost uniformly devoid of distinctive findings Frequently the roentgenograph is not abnormal but in a percentage as high as twenty per cent of the cases definite changes will be revealed and these may vary from small calcareous foci to extensive infiltrations and lymphadenopathies even though the child's general health has appeared to be very good In older children with limited calcareous lesions the tuberculin test may produce no reaction but these lesions usually are presumably healed and rarely active or menacing It may be said that such lesions discovered by these procedures in apparently healthy children are almost always tuberculous and in very few cases will it be necessary to conduct exhaustive clinical investigations to determine the point

Treatment of Tuberculosis in Children

In principle this does not differ materially from the treatment of adults but since the threat to health of any tuberculous lesion is a purely relative matter depending on an analysis of the individual situation the treatment of children merits consideration of itself The lesions following primary infection are identified more frequently at this time of life and sometimes it is stated that they are uniformly benign self healing and never require treatment Although in many cases factors other than medical management may determine the fate of the child this extreme view is not warranted If one recognizes that fatalities are relatively more numerous among infected infants than among infected adults and that the apparently benign lesions of childhood may be the origins of serious tuberculosis in adolescence and later then one is not justified in taking a fatalistic and indifferent attitude On the contrary there is in my judgment good reason to believe that proper management will go far in many cases toward preserving the child's immediate and later health

Classification of tuberculous children for treatment should not be too formal but clinical discrimination is necessary Among the groups to be considered are these

(1) Children who react to tuberculin but in whom no lesion can be demonstrated In the majority of these the lesion is slight and localized mainly in the bronchopulmonary nodes and heals without any definite treatment This represents a group most of whom go through life con

tinuing to react to tuberculin but with no clinical tuberculosis If the subject is an infant or a young child the relatively greater danger of disseminating tuberculosis should not be ignored and every effort should be made to keep the child on an ideal pediatric hygienic routine Such a child had better be under continued medical supervision It is unwise to instill the parents with anxiety but sensible to advise a roentgenograph of the chest at intervals of three to six months depending on the original opportunity for severe infection Older children likewise should have medical supervision emphasizing the need of extra rest during the early months after infection if the date of this can be estimated The roentgenograph of the chest every six months and later once a year is a safe guard With the possible exception of the time shortly following the first infection there is no experience to justify excluding such children from school or other normal activities The important point in the management is the institution and maintenance of an ideal routine to promote and preserve the general health The native resistance of the child may be counted upon to avert the development of clinical tuberculosis in a great majority of cases

(2) Children with demonstrable but localized and apparently healed lesions The management of these children provided the general health is good does not differ from that of the previous group Impairment of nutrition and a tendency to excessive fatigue in a young child may warrant taking him out of school temporarily and keeping him in good home conditions or sending him to some different environment like a summer camp where under intelligent supervision the building up of his general health and resistance may be a material factor toward preventing later progress of the disease Pediatric supervision again is to be emphasized The treatment of these children in fresh air schools of late has lost much of its popularity which is warranted if reliance is placed alone on fresh air Not this but an intelligently adjusted routine of rest proper eating recreation and study are the important factors The question sometimes is raised whether periodical blood counts and estimations of the erythrocyte sedimentation rate are of value in detecting renewed or impending activity of the lesions Sometimes these tests prove to be useful but the negativity of the findings is so customary that the procedure cannot be recommended as a routine The general health of the child and the roentgenograph of the chest at intervals of six months to one year are the most reliable guides

(3) The child with freshly developed and demonstrable lesions large lesions or manifestly active tuberculosis In the cases of manifestly active disease the treatment by rest is essentially the same as that

employed for adults (see in a later section) In a few cases even among young children collapse of the lung by artificial pneumothorax may be indicated because of excavations developing in the lung Radical operations such as thoracoplasty however are advised rarely The great tendency for the disease to settle in the mediastinal lymph nodes of children largely determines the smaller need for collapse of the lung The formal rest cure either at home or in an institution is advisable for lengthy periods in these cases Recession of the pulmonary and lymphatic lesions is observed frequently The inevitable slowness of healing of tuberculosis requires that treatment be continued for one to two years in severe cases even more time may be required before any degree of security can be anticipated In the milder cases the same fundamental principles prevail and the cases are to be judged according to the extent of the lesions the age of the child the general constitution the home environment and the clinical manifestations As in the case of adults symptoms alone are not a safe guide for the type and duration of treatment Even in the asymptomatic stages often it is advisable to continue a strict routine of rest and limited activity until healing is well established Reliance is placed on changes in the lesions demonstrated in the roentgenograph and on the physicians understanding of the rate of healing Because of the known tendency of infected children to break down with progressive tuberculosis in adolescence the advisability of observation during these critical years is obvious and this is particularly true when the child harbors gross lesions even though these seem calcified In the latter case a roentgenograph of the chest every three to six months is indicated Meanwhile every safeguard to preserve and enhance good general health should be enforced

Prognosis of Tuberculosis in Children

Tuberculous infection acquired in childhood is a definite threat to health and life Among 453 infants and children up to the age of sixteen observed by Wallgren in Goteborg Sweden 35 died within the first few months after the primary disease manifested itself He found that the younger the child the poorer is the prognosis and that most of the deaths occurred in the first three years Most of his cases of tuberculous meningitis occurred one to two months after the primary onset rarely after three months Some contend that the primary lesions almost uniformly are benign While these in themselves are seldom the cause of fatality the same cannot be said of the immediate or late extensions from them The situation is somewhat analogous to syphilis in that the

primary chancre alone seems innocent enough. In addition to the experience of Wallgren, that of Miriam Brailey in Baltimore reveals an important side of the picture. She observed 223 children, 91 white and 132 colored, who became tuberculin positive before two years of age and who were followed one to eight years. Twenty eight per cent of the children admitted to the hospital with parenchymal lesions died during the first year of observation. Among those showing no evidence of parenchymal involvement the mortality for white children during eight years was 2 per cent and for the colored 12 per cent. Mortality was twice as high for infants known to be infected before six months of age. The experience of Edith M Lincoln at Bellevue Hospital has paralleled closely that of Brailey. Statistically, Drolet calculated that in New York City in 1930-3 the annual tuberculosis fatality rate among *infected* infants under one year of age was 1 297 per 100 000, which was five to ten times that prevailing among adults. Among older *infected* children Drolet's calculated annual fatality rates were as follows for these years: children under five 430 per 100 000, 5 to 10 52 per 100 000, 10 to 15 35 per 100 000. Thus it is seen that the infection does not prove fatal as often between five and fifteen as it does in later life. However, if one accepts the view that much of the tuberculosis among adults is due to infection acquired in infancy or childhood, the serious implication of the disease in these early years is evident. Already I have stated the conviction that the prognosis can be bettered by careful supervision and management of the tuberculous child.

Pathological, Functional and Clinical Correlations in Pulmonary Tuberculosis, Especially in Adolescents and Adults

In contrast to the great tendency of lymphogenous and hematogenous dissemination of the infection in young children and the relative freedom from disease in later childhood years, adolescence and early adult life bring a liability to disabling and fatal tuberculosis which plays its chief role in the lungs. The lesions appear with increasing frequency after the age of ten or twelve, somewhat earlier in girls than in boys, and earlier in negroes than in whites. Fellows and Reid, analyzing the results of annual x ray examinations of employees of the home office of the Metropolitan Life Insurance Company, averaging from 11 500 to more than 14 000 people, have found the incidence of newly developed tuberculosis in those who were apparently healthy a year previously to vary from 57 cases per 10 000 employees per year in 1930 to 20 in 1938, the decline having been progressive. Among men no new tuberculous lesions

were found developing after the age of 39 and among women very few after the age of 29 In both sexes 68 per cent of the "new lesions" developed between the ages of 20 and 29 and 92 per cent between the ages of 20 and 35 Such experiences which have been accumulating in recent years indicate that active early pulmonary tuberculosis arises most often between adolescence and the age of 30 or 35 This is true whether the lesion represents an awakening of the old latent infection or a new infection from without The younger the person the more likely is the early lesion to be exudative i e a small patch of tuberculous bronchopneumonia This feature is to be emphasized since an appreciation of the potentialities of the early lesion is of such great importance in prognosis and treatment From the clinical point of view there is little or no difference whether the responsible infection was exogenous or endogenous primary or secondary the same observation and treatment are required in either circumstance

Since there is reason to believe that most early infiltrations when first identified represent extensions from lesions which may have existed from a few months to many years before obviously it would be desirable to anticipate the development and prevent it It has been found well nigh impossible however to distinguish between those dormant foci which are likely to become active in adolescence and early adult life and those which continue permanently innocuous In only about 15 to 20 per cent of people some physicians claim more reacting to tuberculin can any pulmonary or lymphatic lesions be detected by x ray these as a rule being more or less calcified remains of the primary complex Such sizable residues presumably represent lesions which at their height were quite extensive and which might be suspected to lead more often to pulmonary tuberculosis later in life This seems to be the fact during adolescence particularly in young girls since Pope found such young people developing significant pulmonary disease three or four times as often as those with previously clear chests by x ray examination Fellows however has not observed a continuation of such consequences after the age of seventeen In some cases apical lesions can be detected by x ray which may be the source of progressive disease These often appear to be the remains of hematogenous foci which may have been initiated shortly after the primary infection in childhood to stop then and remain latent for long periods of time They may show as apical scars or nodules some of which may have a calcareous density Tuberculin negative adolescents and young adults are a little more likely to develop the early infiltration after their first infection at this time of life than those who previously were tuberculin positive and had clear chest roentgenographs

The time required for the development of the early infiltration is difficult to determine because of its symptomless character and this can be estimated only by roentgenographs made at intervals Judging by my observations the time usually is short in young people frequently within six months and in some cases within a few days to several months

Symptoms of the Early Infiltration

The striking character of this lesion is the absence or scarcity of symptoms I have seen it develop in young people who just previously had gained five to ten pounds or more in weight and who had experienced a period of unusually good general health Others report that they have had unusual fatigue particularly toward the end of the working day and that they have been slowly losing a few pounds in weight The symptoms are not in any way peculiar and usually are attributed by the patient to over work or some other casual cause It is exceptional for these patients to have fever but some have a slight acceleration of the pulse particularly in the evening A symptom which occasionally may arrest the patient's attention is pain in the chest This is of sharp or dull intermittent or persisting character often over the site of the pulmonary infiltration and ascribable to the involvement of the pleura Very infrequently patients notice a small amount of blood in the sputum shortly after the inception of the early infiltration I have not observed it at the very inception and it is doubtful whether this occurs before there has been at least a minute ulceration of the focus into the bronchus likewise there is no sputum except perhaps a very small amount of mucoid discharge

Physical and Roentgenographic Signs of the Early Infiltration

Since the lesion is of recent origin small and localized the signs are scanty and in many cases completely lacking The most significant sign if it is elicited is rales and these are confined to a small area of the chest wall immediately overlying the lesion It is not unusual to find them circumscribed in an area two or three centimeters in diameter The *roentgenographic* shadow is the most important finding and by and large is the only means of surely detecting the lesion The shadow is a small patch of soft mottling or clouding or sometimes a small rather round circumscribed faint density depending on the predominating tissue reaction Minute infiltrations easily may escape even this method of examination

Likewise the *laboratory findings* at the inception of the early infiltration are as a rule not very helpful It is not logical to expect to find tubercle bacilli preceding the ulceration of the lesion into the bronchus However ulceration often occurs early even though the peripheral limits of the lesion do not extend simultaneously In 72 per cent of 50 minimal cases Stiehm found tubercle bacilli in the gastric contents Tests of toxemia or of other disturbances reflected in the differential count of the white blood cells and the erythrocyte sedimentation rate usually are within the limits of normal although a slight or moderate deviation may be noted

The most important thing is to appreciate the dynamic potentialities of the early lesion and the great variations in time between different phases The lesion in young people particularly in young girls and more especially in young negroes is with few exceptions of an acute localized bronchopneumonic character while in older people it may have more of a chronic granulomatous structure The former because of its character and setting in the young person tends in the majority of cases without treatment to progress with central caseation and ulceration into the bronchus The latter may do likewise but more slowly The former if regressive may undergo rapid absorption and the patient never is aware of its presence The latter also may come to a standstill by fibrous encapsulation without ulceration likewise without symptoms Such phases almost always are subclinical and would be little known were it not for the information yielded by the periodic examination of apparently healthy people

The subsequent phases of pulmonary tuberculosis vary in infinite ways and directions If progressive the premominant development may be acute or more usually chronic bronchogenic phthisis Since it is important for the physician to comprehend and correlate the changes several of these developments will be described but it must be understood that they are only a few of the many possibilities

(1) *Acute Bronchogenic Tuberculosis* — This may develop at any age but it is seen more commonly in young people and in negroes It does not appear de novo but is traceable to some preceding lesion usually the early infiltration The acuteness often is ascribed chiefly to the marked hypersensitiveness or allergy of the tissues which consequently react with intense and rapid inflammation Allergy no doubt is important but Grethmann s pathological demonstrations at Bellevue Hospital convince me that local physical factors play an equally large and often larger part the factor of massive infection with large numbers of tubercle bacilli is of very great importance The acute changes of the early infiltration are

observed best by roentgenographic examination every week or half week after the lesion is identified When these occur the density representing the bronchopneumonic focus widens as a spreading diffuse cloudiness with soft hazy borders Rales for the first time may be elicited although their continued absence is not rare The patient may still be free of fever and other constitutional symptoms but the erythrocyte sedimentation rate may become moderately accelerated and the polymorphonuclear leucocytes and monocytes of the blood may increase The peripheral extension of the pulmonary inflammation practically always is found to be associated with central caseous necrosis which may start within a relatively few days and become well marked within a few weeks

Ensuing liquefaction then may convert the center of the lesion into an abscess containing as much as several drams of thin creamy pus bearing myriads of tubercle bacilli Now if this ruptures into a bronchus the abruptly liberated contents may be aspirated easily back into the healthy parts of the lung particularly during sleep when the cough reflex is not very active or by the deep inhalation which must precede cough The chance of the aspirated material entering the alveoli depends on its physical consistency as proved by the experimental work of Archibald and Brown Thick coherent mucopurulent matter does not gain easy access to smaller air passages but thin freely flowing fluid penetrates readily and deeply during inspiratory widening of bronchioli and alveoli

Such sudden and massive infection leads within a relatively few hours to an intense inflammatory reaction or acute tuberculous pneumonia in its earliest phases the appearance varying from that of so-called gelatinous pneumonia to that of acute hemorrhagic bronchopneumonia The patient who previously had few or no subjective symptoms suddenly falls ill with chilliness or even a severe rigor to be followed by rise in temperature to 103 F or 104 F a feeling of congestion in the chest and cough with expectoration of small to moderate amounts of mucopurulent sputum at first of a greenish odorless character later yellow Subsequent developments are rapid and the patient may experience a hectic fever rapid loss of weight moderate to severe sweating at night increasing weakness anorexia and other severe symptoms of tuberculous toxemia The pneumonic lesions are prone to caseate and break down rapidly so that in addition to extensive solidifications new cavities form within the space of a few weeks Coincidentally the sputum increases in amount to a few ounces or even six or eight ounces in the day teems with tubercle bacilli and may be mixed with blood Since the vessels may be rapidly occluded large hemorrhages are not as common as in the chronic types

Rapid breathing is a manifestation of the toxemia as well as the progressive reduction of the pulmonary reserve Various complications may appear such as pleurisy or laryngitis In fulminating cases the patient may die within six or eight weeks of the first subjective symptoms The physical signs of course become easily detectable During the early engorgement of the lung dullness and diminution of breath sounds with crepitant râles and limitation of motion of the chest wall on the affected side are observed to be followed in a few days or later by the signs of consolidation and excavation in the areas affected usually adjacent to and below the excavated early infiltration While the complete lung or lobe may undergo consolidation more usually this is confined to smaller sections because the process is a confluent tuberculous bronchopneumonia

The roentgenograph likewise shows the speedy changes the new areas of involvement first appearing as more or less extensive clouding of a diffuse or mottled character later merging into a dense completely homogeneous shadow which may be seen to outline clearly the limits of various lobes The process of caseation cannot be distinguished in the roentgenograph until sloughing leaves behind cavities which appear as rarefied areas with irregular ragged walls Often the excavations at first are multiple and small and are to be detected by the increase of the mucopurulent sputum the finding of coarse râles where previously they were crepitant and the appearance in the roentgenograph of small honey combed rarefactions

(2) *Subacute Bronchogenic Tuberculosis* —That the florid forms of phthisis are not the commonest sequences of the early infiltration probably is due to its predominantly early ulceration before a large central abscess has formed In most cases the change is slow and gradual In some there may be a slight or moderate expansion of the lesion while in others the periphery may recede while the central caseous mass slowly sloughs out This then if progressive often leads to the first manifestation of symptoms and to subacute forms of bronchogenic phthisis Whether the secondary lesions produce predominantly local or constitutional symptoms depends on their intensity and extent Slight local extensions may still remain subjectively subclinical The patient will notice only a morning cough or slight clearing of the throat which if he does not swallow the discharges results in the production of a little yellowish mucopurulent sputum containing tubercle bacilli Constitutional impairment still is slight or lacking which is one reason for the failure of the patient to be impressed by the cough Occasionally the sputum may be bloody with small streaks or clots or less commonly there may be a free hemoptysis

Physical signs still are slight or lacking although the possibility of

eliciting rales now is greater The roentgenograph which originally showed only a small localized patch of mottling now may reveal a small central rarefaction and around the periphery scattered soft mottling representing the bronchogenic extensions As time goes on the original cavity may enlarge and any of the secondary lesions may spread also and become excavated Small bronchopneumonic lesions usually recede larger ones are more likely to progress Subsequently there may be a succession of further bronchogenic spreads but these frequently are interrupted by quiescent intervals During the active stages subacute symptoms are observed in most young people while in later adult life chronicity is more prominent Subacute manifestations simulate grippe particularly when after a febrile period the patient feels better The pulmonary cavity now may have grown larger but the elimination of its caseous contents alleviates the toxemia

The continuousness intermittency and intensity of the recrudescences is variable After the development of the first pulmonary cavity partial *resolution of the surrounding inflammation may take place and a stationary* phase may ensue in which the cavity continues to discharge a little tuberculous pus without further bronchogenic extension of the lesions Except for the continuing cough or clearing of the throat the patient s general health remains good Quiescence may continue for months or years to be interrupted perhaps by a hemorrhage the first event to arrest serious attention Aspiration of blood containing tubercle bacilli washed from the cavity into healthy parts of the lung now may cause the first more or less severe constitutional symptoms and convert the quiescent cavernous case into an acute tuberculous bronchopneumonia Barring this successive or continuous extensions are responsible for the familiar picture of the gradually failing patient who experiences together with the cough and expectoration slow wasting of the soft tissues failing strength and energy lo s of appetite and afternoon fever Complete prostration is not the rule until the advanced stages of the disease are reached and one often is struck by the tolerance of patients for the mild but long protracted toxemia The physical signs during these progre sive stages become more pronounced and typical

In the subacute lesion the walls of the cavities are not well organized and not surrounded by dense solidifications consequently the most common and most suggestive sign is the finding of moderately coarse or coarse moist râles sometimes with a bubbling or even consonating quality The roentgenograph portrays the changes most clearly the excavated areas appear as irregular or round rarefactions with walls varying from several millimeters to several centimeters in thickness Surrounding

lesions which now may be partially fibrotic appear as more or less nodular densities mingled with linear striations Fibrous retractions if any are slight Scattered irregularly about and below the cavities lesions of varying age give rise to shadows of soft mottling localized areas of homogeneous clouding or fine nodular densities

(3) *Chronic Bronchogenic Tuberculosis* —The transition between the acute and subacute forms on one hand and subacute and chronic forms on the other is not distinct in fact it is best not to attempt to visualize clear cut divisions since the phases of tuberculosis too often are mingled Nevertheless the well known characteristic of tuberculosis to become chronic disease warrants attention Chronicity of course represents a more or less successful defense reaction on the part of the body The time required for the defenses to become mustered sufficiently to retard or arrest the infectious processes and establish chronicity or arrest varies from a few months to many years The changes which occur in the lungs during the interval may be slight and few or extensive and numerous and the clinical picture varies accordingly The early infiltration may become stabilized after the first phase of caseation liquefaction and excavation standing now as a localized chronic fibrous walled cavity with a few surrounding fibrous tubercles and giving rise to a slight or moderate chronic morning cough This may be tolerated well even under normal living conditions for many years

As a rule however repeated small bronchogenic extensions occur The patient s awareness of the condition depends largely on his subjective sensitiveness to mild toxemia which may represent itself only as temporary malaise The phlegmatic person inured to hardship may be wholly unconscious of trouble until the final collapse comes while the more delicate sensitive patient is disturbed easily and may even be regarded as hypochondriacal The slow continuous or periodical creeping ahead of the pulmonary lesions and the associated reparative fibrosis sooner or later is followed by the development of surrounding emphysema The lungs gradually become overdistended and lose their elasticity bronchi and blood vessels are distorted while the capillary bed is reduced The thoracic cage becomes widened more or less immobile and the result is a functional depletion manifested by dyspnea and chronic anoxemia and their consequences In some of these cases the healing of the lesions becomes wholly effective as the respiratory embarrassment becomes disabling

Another common example of chronic fibroid bronchogenic phthisis i that which develops after a comparatively early stormy course In these cases the early infiltration may break down soon giving rise to extensive

and perhaps massive bronchogenic disseminations which after a period of some years are held in abeyance and undergo more or less fibrosis This form often is predominantly unilateral with massive fibrosis of the lung and pleura resulting in marked retraction of the trachea heart diaphragm and chest wall Such patients if the opposite lung remains reasonably healthy do not as a rule suffer evere respiratory dysfunction or disabling toxemia but are more likely to have a chronic cough with sputum containing tubercle bacilli originating from the chronic cavity

Repeated hemoptyses are observed in many cases but it is remarkable how some of these patients tolerate severe hemorrhages without serious bronchogenic dissemination of the infection The reason is that the wall and lining of the cavity is made up of fairly healthy vascular granulation and fibrous tissue with a minimum of active caseous necrosis consequently a gush of blood is less likely to carry with it numerous tubercle bacilli On the other hand it is in the chronic fibroid case that the occasional sudden fatal hemoptysis is observed more often due apparently to weakening of the walls of the blood vessels which are not as often obliterated as they are in the vicinity of an acute lesion In general it may be said that in chronic fibroid tuberculosis physical signs are of the most classical character when massive fibrosis and shrinkage predominate and of a very indeterminate sort when there is a severe grade of emphysema to mask other changes

(4) *Hematogenous Forms of Pulmonary Tuberculosis* — During recent years a great deal of new information has been acquired concerning infection of the lungs by hematogenous seeding the original focus usually being in caseous lymph nodes in the mediastinum or elsewhere The participation of the lungs in acute generalized miliary tuberculosis has long been familiar but the part played in subacute and chronic phases only recently has been better elucidated While such pulmonary lesions may be and frequently are associated with lesions elsewhere in the body this is not necessarily the case as explained previously The extent of the pulmonary involvement depends of course on the degree and frequency of the hematogenous seeding This may be only momentary perhaps shortly after the establishment of the primary complex and the liberated bacilli may be few Consequently the tubercles in the lung may be scarce some may become absorbed and others latent In the latter event as suggested by the studies of Tendeloo Simon Wurm and others the persisting lesions may be found only in the pulmonary apices it is these which have been shown in some cases to be the source from which bronchogenic disseminations may occur after a lap e of months or many years Heavier insemination may give rise to more numerou tubercle

concentrated often in the upper parts of both lungs These are discrete round lesions visualized in the roentgenograph as a fine or slightly coarse nodular studding symmetrically distributed in the upper third or half of each lung field In still other cases the roentgenograph shows a scattered fine nodular studding sprinkled throughout both lung fields but, as a rule more thickly at the apices

In still others designated by Grethmann as protracted hematogenous multiform tuberculosis, there is presumable evidence that tubercle bacilli are fed into the blood stream at irregular intervals and perhaps in clumps as well as singly resulting in the formation of a small to moderate number of irregular lesions varying in size from submiliary to one centimeter in diameter and in character from grey tubercle to complete caseation In these cases seen more commonly in negroes and young children the protracted dissemination is likely to involve also other parts particularly the serous membranes lymph nodes spleen liver and kidneys The course seems to depend largely on the number of foci implanted The protracted form of Grethmann usually terminates fatally but not until the lapse of three to six months sometimes later Subacute slight or moderate pulmonary invasion causes symptoms mainly due to the toxemia and constitutional disturbances Chronic forms in which there is a gradual partial absorption fibrosis and occasionally calcification of the interstitial tubercles may account for long periods of poor general health without localizing symptoms and eventually may lead to a more or less advanced and disabling grade of pulmonary fibrosis and emphysema Any of these forms at any time may be transformed into bronchogenic tuberculosis by the process of caseation and ulceration Only in this event do patients show tubercle bacilli in the sputum On the contrary it is readily seen that in acute generalized miliary tuberculosis tubercle bacilli seldom are demonstrated in the sputum because the patient dies from overwhelming toxemia before sufficient time has elapsed to permit ulceration of the lesions

(5) *Non caseating Hematogenous Forms of Pulmonary Tuberculosis* — Pinner has called attention to chronic forms of hematogenous tuberculosis in which caseation is minimal or entirely absent The process may be more or less generalized or confined predominantly to the lungs in which the lesions give the appearance of an extensive largely interstitial linear and nodular fibrosis radiating from the hila Into this group some would place the striking cases of Boeck Besnier disease or sarcoidosis while others consider the latter to be an entirely different disease because of the usual failure to demonstrate tubercle bacilli in the lesions the lack of caseation and the insensitiveness of the tissues to the tuberculin test

(6) *Healed and Arrested Forms of Pulmonary Tuberculosis* — There are several interesting correlations in this connection that deserve mention Healed and calcified residues of an old primary complex or a few old hematogenous tubercles scattered in the lungs rarely give rise to detectable physical signs Because of the density due to the calcific changes they are shown in the roentgenograph In the case of minute foci there may be a phase between the partial absorption of the lesion and the calcification of the caseous residues when even the roentgenograph fails to reveal it After some years it may come again into view because of the calcification It is a frequent observation that tuberculosis may remain well arrested and healed even though it may be possible throughout the remainder of the patient's life to elicit rales in the involved area A study which I have reported indicates that these persisting râles are due not to specific inflammatory reaction about the tuberculous foci but rather to an accumulation of nonspecific catarrhal exudate in the alveoli and bronchioli related to the emphysema fibrosis and mechanical distortion which are accompaniments of the healing process If fibrosis is extensive the vascular supply may be altered as described years ago by Turban and later by Pagel Bleeding of slight amount from such sources is not uncommon occasionally it is profuse It is seldom dangerous since the mechanism does not involve the ulceration and excavation of the tuberculous lesion

Tuberculosis of the Lungs With Special Reference to Adolescents and Adults

Onset

Conceptions of the onset of pulmonary tuberculosis have changed materially in recent years since the behavior of early lesions has become more familiar It must be repeated that the actual onset of the disease frequently is not attended by any symptoms of which the patient is conscious Sometimes a lesion develops and runs its course to healing without producing subjective symptoms Indeed there may be a succession of secondary infiltrations before the symptoms become subjectively evident In other words symptomatic onset may be far removed from the actual onset This varies greatly and the interval may be short or long Frequently after the patient has come to understand the nature of his disease he will be able to recollect events which previously he did not connect but which help to piece out a clinical picture of considerable duration

Since in practice the physician's advice usually is not sought until definite symptoms make this necessary it is desirable to consider the different clinical manifestations as they are likely to be encountered These are variable and cannot be classified strictly In some cases the first suggestive symptoms are those of general toxemia while in others the toxemia is minimal and local manifestations predominate The first signs of toxemia may develop slowly and insidiously or acutely and alarmingly The insidious onset extending over a few or many months is marked most often by gradual loss of weight and energy the tendency to tire easily and sometimes by anorexia The patient is not impressed by these symptoms and the loss of weight may be discovered inadvertently This he attributes to the fickleness of his appetite or some external cause such as poor food Likewise the loss of energy and staying power frequently associated with some nervous irritability is ascribed to the burden of work bad weather loss of sleep or anxiety over some personal trouble Rather characteristically the patient may arise in the morning feeling fairly energetic after the night's rest only to find his strength and energy failing much earlier in the day than is customary eventually the night's rest does not bring even this refreshment Often medical advice is not asked until a friend or employer notices the patient's decline and makes the suggestion Otherwise the patient still unaware may gradually recover apparent well being only to have a repetition of more or less similar symptoms some months or years later

Subacute constitutional manifestations at the onset commonly resemble those of grippe or influenza The patient previously may have been healthy or noticed only slight fatigue and loss of weight Then possibly following an acute cold or some unusual exposure or strain he becomes prostrated with general malaise fever perhaps some aching in the back and a little headache and he notices at the same time some cough and expectoration The symptoms may be severe enough to cause him to remain in bed or at least at home where following a rest of a few days or several weeks the constitutional symptoms gradually subside The cough seemingly attributable to simple bronchitis does not disappear as quickly or may grow worse and as a rule the patient finds himself unable to regain his former health as quickly as he had expected An insidious course may now continue or there may be a recurrence of the grippe like symptoms The stubbornness and repetition of these episodes with slowly failing strength sooner or later causes the sufferer to seek help but it is remarkable how he may persist in his attempts to resume normal life until the disease has invaded the lungs widely and left little chance for recovery

A peracute and abrupt onset of general symptoms while much less frequent may occur at any time of life but is noted more often in young people and particularly in young negroes Careful questioning often elicits the information that preceding the acute onset the patient had a slight persistent or recurring cough which to him did not appear related The sudden illness then may be initiated with a mild chill palpitation of the heart sweating and high fever The severity of these symptoms and the development of a cough and possibly pain in the chest lead to the suspicion that he has severe acute bronchitis or even pneumonia Lacking such a striking onset other patients may be impressed by general symptoms which affect them in some peculiar way One may have disturbances which are mainly digestive with loss of appetite dyspepsia and constipation another may be disturbed by an unaccustomed sweating at night while still another will notice that some special ability or skill is failing The last for instance may notice an unsureness of his occupational skill the loss of effectiveness in some sport or an aversion for his customary social pleasures

If toxemia is of only minor degree some local symptom may be relatively conspicuous Cough is one of the most common and often is the only one to attract attention While it may be a part of the continuation of an acute cold more often it is not so introduced but develops as a gradually increasing irritation in the throat or bronchial tubes Usually it is noticed in the mornings after awakening and particularly after breakfast but the irritation may recur occasionally throughout the day It varies in intensity and may be accompanied by the production of mucopurulent sputum Frequently attributed to a cold irritation from smoking or some other trivial cause the cough alone may not bring the patient for diagnosis but only when other symptoms are associated Among these one of the most important is hemoptysis This again may be antedated by some other vague symptoms but not uncommonly it is the first sign alarming the patient The hemorrhage may come without warning or may be preceded for a few days by streaking of the mucopurulent sputum

Similarly a sharp pain in the side caused by pleurisy may be the first arresting symptom and this is particularly impressive when it is accompanied or followed by fever prostration dyspnea and other symptoms caused by the accumulation of a serous effusion The pain may be transient recurrent or continuous and its pleuritic character may be suggested by the aggravation upon deep breathing While pleurisy may direct attention to already existing pulmonary tuberculosis it may also antedate the development of this by many months or years

An onset with severe and alarming symptoms may be related to the collapse of the lung by the perforation of the visceral pleura from an underlying tuberculous lesion Previous symptoms of pulmonary disease may have been present but in some cases the general health is excellent until the patient suddenly experiences a sharp stabbing pain in one side of the chest and becomes short of breath This may be followed quickly by the development of fever prostration and increasing respiratory distress and cyanosis In a few instances the patient may be found in shock or almost moribund

Tuberculosis of the larynx is a sequel of pulmonary tuberculosis but the symptoms of the latter may be so slight that they were not apparent previously or related so closely in time that they were not distinguished The first symptom therefore may be hoarseness or huskiness of the voice simulating simple catarrhal laryngitis particularly if the patient has had an acute cold The tendency however is for the hoarseness to persist particularly as the larynx becomes fatigued or irritated by talking often it is accompanied by an annoying tickling or dryness without soreness Sooner or later the patient becomes aware that he also raises a little mucopus which at times may be stained or streaked with blood Sometimes the laryngeal symptoms completely dominate the picture before the diagnosis is made and in the interim severe soreness and even dysphagia may have developed

Fistula in ano may be the first subjective difficulty although this too is a secondary lesion The swelling and tenderness near the anus usually is thought to be due to a hemorrhoid and the patient may not be aware of its true nature until it ruptures to the outside discharging pus Not all such perirectal abscesses are tuberculous particularly if the pus is foul In other cases secondary tuberculous involvement of the intestine may cause the first subjective manifestations in which case diarrhea and colicky pains may cause the patient to seek attention

These initial symptoms are emphasized because of their frequency but one should not overlook the fact that any tuberculous lesion anywhere in the body may represent an infection having its origin in the thorax Therefore any such discovery invariably should direct attention to the chest where a proper examination may reveal the source of the trouble

Symptoms

The mechanism of production of symptoms of pulmonary tuberculosis has been described in part These arise mainly in several ways by the absorption into and diffusion through the circulating blood and lym

phatic streams of the toxic materials elaborated by the tubercle bacillus and arising from broken down necrotic tissues by reflex neurogenic influences and by local changes depending on the site and mode of extension of the lesions. Nervous reflexes are not often apparent subjectively and symptoms of the other two classes are of greater importance.

Malaise is one of the most constant symptoms. It is represented by a feeling of fatigue, weakness, loss of energy and occasional faintness on account of which the patient has a chronic urge to avoid physical or mental effort. The symptom is not always disagreeable unless the patient is obliged to exert himself in spite of it and may at times manifest itself as a laziness or disinclination affording a pleasant excuse for rest and inactivity. Often it is relieved easily by resting and as a rule it does not amount to complete prostration except in the acute and advanced stages. Malaise is not necessarily associated with fever.

Loss of weight is almost inevitable in cases of progressive disease. In some it is an early and perhaps only symptom, in which event usually it is gradual with a loss of two or three pounds during the course of two weeks or more. But it must be emphasized always that at the very onset of pulmonary tuberculosis there may be no loss but even a recent gain. In the insidiously progressive cases the loss continues slowly, often totalling ten to twenty pounds in a space of six or eight months; during febrile periods this may be accelerated greatly so that ten or fifteen pounds may be lost in a month or two. In other cases going on to slow chronicity impaired nutrition is not so remarkable since it is represented not by a loss but rather by a failure to gain during the growing period and afterwards. Such patients then may remain spare and thin during many years, this being considered a constitutional characteristic. Loss of weight is mostly at the expense of fat although there may be also an obvious impairment of muscular development. Initially the impairment is due almost entirely to the toxemia but later some other mechanism such as deficient absorption after the development of intestinal tuberculosis may contribute. The loss does not always run parallel to the advancement of the pulmonary lesions. Thus a patient under treatment in bed may have increasing infiltration and excavation of his lungs with no loss in weight or he may actually gain in weight. In the late stages particularly after complications have arisen wasting may be extreme, hence the name phthisis or consumption. Subcutaneous fat and muscular tissue may dwindle gradually until the skin hangs loosely over the skeleton and this state may continue for many months or even several years before the patient dies.

Fever likewise is one of the most constant symptoms of progressive

tuberculosis although at the inception its usual absence is conspicuous The patient may not be subjectively aware of fever in fact a feature of this toxemia is its failure to produce the subjective prostration and feeling of illness so commonly observed in other infections A patient with tuberculous pneumonia running a fever of 104° F to 105° F often asserts that he feels fairly well The symptom therefore often is noted only by routine recording of the temperature This is done preferably with the rectal thermometer every four hours during the day and early evening oftener when specially indicated The characteristic finding is a normal or subnormal temperature in the early morning hours with a gradual rise during the day until in the late afternoon or early evening it ascends to a variable degree in the moderately active case this varies from a few tenths of a degree to one or two degrees The cycle may be repeated fairly regularly for many days and in progressive cases for many months Improvement is accompanied usually by a slow recession and the gradually downward trend may be definite only after the lapse of weeks Meanwhile a little digestive or emotional disturbance or unaccustomed activity may cause another slight rise during one or several days Finally the temperature remains constantly a few tenths of a degree below normal throughout the day accentuated perhaps by a more decided subnormality in the early morning In more severe and acute cases the afternoon rise may attain 103° F to 104° F for many days the curve usually being of a remittent type with recession during the early morning Very acute cases have hectic fevers which for days or weeks may rise to 104° F or 105° F daily in a few instances higher Subsequent quiescence if it is attained may be disturbed by morning subnormal temperature during which the patient feels weak and enervated In chronic advanced cases fever may be irregular and occasionally hectic sometimes with a change in the cycle evidenced by a high rise near midnight or in the early morning hours Since tuberculous toxemia is not especially unpleasant the patient may feel that he has lost his fever when it has subsided only partly

Chilliness is not a common feature of any phase of this disease It may be noted at the onset of acute progressions but real rigors are rare except in the terminal or complicated phases when secondary pyogenic infection may play a part The frequently observed daily rises of the temperature to 103° F or 104° F usually are not attended by chilliness Similarly an outbreak of *herpes* of lips during any of the febrile attacks unless associated with some secondary infection is rare

Sweating occasionally is a complaint during the febrile periods The symptom when it occurs is noticed most often during the late afternoon

or night as the temperature subsides Slight sweats make themselves evident over the skin of the chest and back while severe ones are general and may be drenching so that the patient awakes feeling cold and clammy This symptom is not a feature in the diagnosis of early disease and is not complained of very frequently by patients under modern treatment

Cardiovascular and *circulatory manifestations* of toxemia may be represented in a number of ways the most common being tachycardia This symptom parallels the temperature curve roughly being most pronounced as a rule during the latter part of the day However it is noteworthy that the pulse usually is more unstable than the temperature and long after the latter is normal the rate may remain between eighty and ninety per minute in men and perhaps ninety and one hundred in women during the afternoon During febrile periods the pulse usually ranges upward from eighty to one hundred and twenty per minute It is seldom irregular but the volume as a rule is small the diastolic pressure usually is normal while the systolic may be as low as ninety or one hundred mm Hg Even though physical exertion may not cause a rise in temperature acceleration of the pulse rate usually is quick and apparent until the disease is brought well under control The circulatory symptom of flushing may in the active case and sometimes in the chronic fibroid case be a subjective complaint This is most noticeable in the face over the malar surfaces and sometimes more pronounced on one side Most often it is coincident with the afternoon fever and it may cause an uncomfortable burning of the skin The circulatory instability likewise may be shown by the flushing of the skin of the thorax on slight superficial stimulation

Cyanosis may be severe in the advanced fibroid case with emphysema and also in the case of acute tuberculous pneumonia Otherwise it is present only in a mild degree or not at all In protracted febrile cases a blueness of the finger tips may be noticeable in the mornings when the patient may complain of coldness and clamminess of the extremities

Gastrointestinal symptoms may be due to the toxemia to reflexes by way of the vegetative nervous system or to actual invasion of the alimentary tract by infection the last being considered under complications The digestive symptoms are prominent as a rule only after the disease has become advanced or during the acutely progressive phases In the early stages there may be slight anorexia a disinclination to take customary amounts of food and a slowness of digestion evidenced by a feeling of fullness eructation and indigestion for several hours after meals The disturbances usually subside promptly when the patient gets the needed rest Less commonly the appetite lags and becomes very fickle

The patient is prone to complain that the food is lacking in quality or in preparation it is difficult to satisfy him and he may experience mild indigestion even on eating small quantities He may have a distaste and intolerance for special kinds of food particularly fatty and so called heavy articles He may be constipated and complain that strong cathartics are required at frequent intervals As a rule there is no abdominal pain or diarrhea unless the intestines become involved in the tuberculous process Vomiting is an uncommon symptom but in some patients may be induced by severe coughing Usually this amounts only to slight regurgitation of food but occasionally coughing and gagging to raise copious discharges from the bronchi nauseates the patient and he may lose one or more of his meals during the day

Urinary symptoms are rare except in the presence of infection of the tract Occasionally women with weak urethral sphincters especially those who have borne children experience difficulty in retaining the urine during coughing

Menstrual disturbances are common in progressive and advanced disease but not during the early phases In young women and girls amenorrhea or scanty flow may be the first clinical manifestation this may be only temporary or last for many months In a few cases women experience menorrhagia but this is not necessarily due to the tuberculosis alone The libido and potentia of tuberculous people are not disturbed greatly even during the active phases of the disease and sometimes not even in the terminal phases The fertility of tuberculous women has been observed by Mathews Downs and others to be somewhat reduced but this is true only during the more active stages and in advanced cases

Nervous and *psychic symptoms* are not conspicuous The irritability associated with the undue fatigue of early tuberculosis may be a feature but this symptom is more pronounced in the chronic fibroid case with emphysema in which the constant anoxemia may be the underlying cause Such patients may be irascible and hard to live with Psychic disturbances are not characteristic The shock occasioned by the knowledge of the diagnosis may be followed by a period of depression such as any other bad news might bring Depressions and a distorted outlook may be a feature because of the prolonged disability confinement and discouragement but these can hardly be considered abnormal reactions It is the general experience that suicidal or other extreme tendencies seldom are manifested by tuberculous patients Dementia praecox was once characterized as the insanity of the tuberculous this seems to be little more than coincidence although Kallman suggests a common biological background such as some unknown tissue inferiority Similarly one can

hardly be impressed by the alleged euphoria of tuberculous patients except in the very late stages of the disease The average patient with early or moderately advanced disease has a quite normal psyche which sometimes may be a little stimulated or a little depressed by the toxemia

Cough is a greatly variable symptom and seldom is a feature of the very early stages It is often perhaps exclusively a morning symptom In most cases it is light or moderate in severity and occurs only as an effort to raise sputum many times there is only a little hacking or clearing of the throat for this purpose In later stages the discharges may be so copious and tenacious as to produce severe racking and exhausting cough it may lead to emesis Coughing may be aggravated also by lesions in the larynx trachea or main bronchi The symptom may be influenced by posture so that the patient usually favors lying on the more diseased side

Expectoration —While in the earlier stages small discharges may be raised unconsciously and swallowed later the cough usually is productive of sputum If the patient rests well at night the discharges usually accumulate and for the most part are eliminated in the morning particularly after the taking of warm food which stimulates the bronchial flow The more active the pulmonary lesions and the more progressive the excavation the more productive is the cough The sputum has only a slightly fleshy odor or none at all It is not foul except sometimes in late stages when there may be a secondary anaerobic infection of the cavities and occasionally where drainage has been impeded by bronchial lesions or distortions

During the first phases of excavation the sputum usually is of a light greenish mucopurulent character When collected this may have a nummular and rather tenacious consistency If the rate of excavation later is retarded the sputum becomes yellowish and later still it may be clear and mucoid containing only a few flecks of coherent pus In a continuously progressive case however the sputum continues yellowish green and may become thin and liquid it may increase to amount to 50 or 100 c c per day exceptionally 200 to 300 c c It has to be emphasized here that sputum production often reflects the trend of the pulmonary cavities but does not necessarily indicate their extent Thus a large fibroid cavity in a quiescent phase may give rise to only a few c c of sputum in a day

Hemoptysis has been reported to occur in some degree in about one-half of the general run of tuberculous cases I have not observed it in the case of the early infiltration before ulceration However after the lesion has become excavated bleeding is not infrequent Slight streaking

The patient is prone to complain that the food is lacking in quality or in preparation it is difficult to satisfy him and he may experience mild indigestion even on eating small quantities He may have a distaste and intolerance for special kinds of food particularly fatty and so called heavy articles He may be constipated and complain that strong cathartics are required at frequent intervals As a rule there is no abdominal pain or diarrhea unless the intestines become involved in the tuberculous process Vomiting is an uncommon symptom but in some patients may be induced by severe coughing Usually this amounts only to slight regurgitation of food but occasionally coughing and gagging to raise copious discharges from the bronchi nauseates the patient and he may lose one or more of his meals during the day

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pneumothorax The symptom is prominent in acute rapidly advancing tuberculous bronchopneumonia and may be the chief complaint in old chronic fibroid phthisis with secondary emphysema In the latter case a few of the patients develop the further symptoms of strain on the right side of the heart cor pulmonale and if this leads to failure the characteristic symptoms of visceral congestion edema of the dependent parts or even general anasarca may result

Wheezing may be a transient or persisting symptom and may be due to lesions in the trachea or bronchi (see on a later page) particularly if the sensation is noticed on one side of the chest This so called asthmatoid wheezing may be heard easily at the open mouth of the patient and in fibroid cases other resonating sounds may be noticed in the throat such as a click synchronous with cardiac systole Wheezing is particularly a feature of some fibroid and emphysematous cases and by some has been referred to as tuberculous asthma In most instances a mechanical cause can be ascertained and there is little reason to believe that the condition is due to a specific hypersensitivity to tuberculoprotein as once supposed

Physical Signs including Roentgenographic Signs

It is well known that the complete range of physical findings may be observed in patients with pulmonary tuberculosis More often than not the examination at the very start of the disease is completely devoid of abnormal findings but as the lesions advance these become apparent in many combinations In the case of recently developed disease usually there are no abnormalities to be discovered by inspection and palpation except perhaps very slight lagging of respiratory movements on one side and slight diminution of vocal fremitus Careful percussion and auscultation disclose the most constant findings namely slight to moderate dullness usually in the upper one third of the chest and a few to a moderate number of fine or moderately coarse rales In many cases one is able to commit himself only on the finding of rales The abnormalities may be detected anteriorly or posteriorly or high in the axillary space a favorite site is the upper one third of the interscapular region on one side The pulmonary apex may be found normal but very common signs are slight dullness here perhaps with a narrowing of the isthmus and a few rales

Alterations in breath sounds may vary from slight diminution to moderate exaggeration and a bronchovesicular quality The existence of cavity may be suspected from the altered breath sounds but more often from the quality of the rales bubbling or consonating With intervening

or pinkish discoloration of the sputum is mentioned at some time by most patients who have a cavity As a rule it is noticed in the sputum raised in the morning but it may occur at any time In other cases the patient may raise only a few bright red clots Others complain of a feeling of warmth in the throat and a salty taste in the mouth to be followed by the expectoration of liquid blood In still other instances he is seized with a fit of coughing or strangling and immediately the blood may issue so rapidly that some of it is swallowed

In only a minority of cases less than one per cent of all tuberculous patients is there immediate exsanguination Such fatalities are observed more often in the chronic fibroid cavitary type of tuberculosis The patient is overwhelmed by the flow of blood and dies from suffocation otherwise death is explained on the basis of spasm of the glottis or some poorly understood reflex The time of hemoptysis has for a long time been a subject of interest particularly as it may be related to physical effort Studies have shown that patients seem more likely to have hemoptyses in the spring and fall of the year Many occur during the early morning hours when the patient may be startled from his sleep which throws doubt on the assumption that physical effort is usually a precipitating cause Menstruation in some women is well recognized as a predisposing cause apparently due to changes in capillary permeability the bleeding may occur just before or during the menstruation

While bleeding may start unannounced patients occasionally have a forewarning such as a feeling of tension in the chest which may subside after the hemoptysis Such sensations before or during the bleeding help in indicating which lung is the source and while the subjective symptom is not to be relied upon completely sometimes it is valuable particularly when collapse of the lung by artificial pneumothorax has to be considered The symptom may continue at intervals of hours days or even weeks When so repeated the quantity at each bleeding usually does not exceed several hundred c c and often indicates only slight oozing Recurrent hemorrhages are seen most often in patients who have chronic fibroid disease Secondary anemia may result and frequently there is a febrile course of varying duration immediately after the hemoptysis The latter often is related to inflammatory reactions in the lung following the aspiration of blood into the lower lobes which in some cases is a trivial and passing event but in others represents a more or less acute secondary tuberculous pneumonia When extensive and progressive this posthemorrhagic pneumonia may be fatal within several months

Dyspnea is not a symptom in the early stages of pulmonary tuberculosis unless this be complicated by a pleural effusion or spontaneous

density usually in the upper one third of one lung frequently below the apex and occasionally in the lower one half The borders are hazy and merge gradually with the anatomical lung markings Tiny shadows may be obscured or show only partially behind a rib or other structure A honeycombed or round rarefied area in the center of the density suggests early excavation in which case other mottlings may be seen in the vicinity or perhaps at some more remote point Later developments may be represented by a more or less rounded thin walled rarefaction which stands alone or in association with irregular mottling elsewhere or the cavity may be in the midst of a dense consolidation which gives rise to an almost complete opacity of the whole lobe Merging cavities are shown by merging rarefactions Pleuritic changes of various sorts may be clearly evident Associated fibrosis may appear at first as light wiry strands radiating from the hilum or enclosing nodular sharply circumscribed densities which stand out clearly because of the surrounding emphysema Dense fibrosis often results in retractions and distortions which are visualized easily and may produce in addition a rather homogeneous clouding of the field Calcareous changes in lesions are revealed by dense nodular appearances which seem to be completely opaque or of a granular character and vary in size from one mm or less to one or two cm The shadows may be round or irregular slightly branched and pointed It is the rule rather than the exception for the roentgenograph to show more extensive lesions than revealed by physical examination

The *sputum examination* carried out as described on a previous page is extremely important When the patient is properly instructed and a specimen carefully collected and skillfully examined tubercle bacilli will be demonstrated in practically all tuberculous cases in which there is a cavity The necessity of repeated examination and of using the more searching methods in cases in which the preliminary findings are negative must be stressed While consistently negative findings are of great importance in differential diagnosis one may expect logically not to find tubercle bacilli in the presence of lesions which are healed or arrested nor in the presence of the early infiltration which has not yet ulcerated In some of these cases the organism may be found in aspirated pleural fluid or other exudates

Pyogenic organisms demonstrated by culture of the sputum represent contaminations from the mouth or possibly secondary invaders in tuberculous cavities The finding therefore is not of diagnostic value except when for some special reason one may suspect that complicating infection such as pneumococcic pneumonia may play a part in the clinical picture The demonstration of elastic tissue fibers or

normal areas other signs may be found in varying combinations such as patches of râles at one or both bases which are related to the secondary bronchogenic disseminations In some cases the original lesions in the upper one third may be devoid of definite signs whereas the secondary disseminations at the base may be more superficial and therefore give rise to clear cut signs The occasional occurrence of an early infiltration in the lower one half of the chest possibly with excavation may be indicated by a patch of râles beneath the breast or in the lower interscapular or axillary region Except in a goodly percentage of the small early infiltrations careful examination will yield in most instances some finding which is definitely suspicious or at least questionable to be confirmed by x ray examination More outspoken and classical physical signs are elicited in the later stages depending on the course

Rapidly advancing tuberculous pneumonia frequently results in a partial solidification of a lobe usually an upper which is detected by a diminution of respiratory movements dullness bronchovesicular to bronchial and amphoric breathing which may be limited by the planes of the interlobar fissures Near the center of such solidifications moist and bubbling râles often give an important clue to the presence of necrosis and excavation In disease of considerable standing neurotrophic changes may be found Over one side of the upper thorax the muscles may be partially atrophied may be found somewhat spastic on palpation and to undergo fibrillary twitching on light percussion The skin likewise may be lacking in tone and the subcutaneous fat may be wasted obviously Muscular wasting and mild spasm or atony may be found related to various nerve pathways in such structures as the tongue face or neck Inequalities of the pupils may be due to irritation of the superior sympathetic ganglia Horner s syndrome is observed seldom

Advanced fibroid phthisis gives rise to the most classical physical findings and by inspection alone one may detect the trouble on account of the unilateral flattening and immobilization of the chest with the associated muscular atrophies Together with retractions of the trachea heart and diaphragm loud harsh and the classically cavernous and amphoric breath sounds cracked pot note posttussive suction and many other signs are demonstrable in such cases If the lesions are predominantly unilateral the signs of emphysema are found in the opposite lung in bilateral cases these signs largely or completely may displace those which ordinarily reveal the tuberculous lesions

The *x ray examination* is presented best by the roentgenograph made in the usual postero anterior direction with the patient erect The characteristic shadow of the early infiltration is an area of irregularly mottled

Diagnosis

The diagnosis of pulmonary tuberculosis and a determination of the clinical significance of the lesions often requires a period of observation lasting for several weeks occasionally longer This is warranted in view of the importance of the decision Conditions should be enforced according to the immediate findings As a rule young people under observation should be confined to bed at once since rapid advancement of the lesions otherwise may occur In older patients with lesions which appear to be of some standing and partially fibroid in character it may be reasonable to allow continuation of most of the usual activities during the observation period In fact this may be essential in order to determine whether there are any signs of activity of the disease under the stress of exertion In the matter of diagnosis one may accept Lawrason Brown s dictum that the practicing physician should have tuberculosis constantly in mind remembering that its clinical manifestations may be most obscure and bizarre In general the possibility of tuberculosis is suggested strongly and should be investigated further under the following conditions (1) In any patient who spits blood unless there is definite evidence that this arises by some other mechanism such as epistaxis Hemoptysis seldom originates in the pharynx or larynx but usually in the bronchi or lung (2) In any case in which there is a cough which persists for more than two or three weeks This may be productive of sputum The symptom is suggestive at all ages but especially in adolescent youths and young adults (3) In the case of patients who report repeated attacks of grippe or pneumonia especially if the duration of the attacks is beyond the expected period of time and if the pneumonia is slow to resolve (4) In any patient in whom there is an unexplained fever loss of weight or abnormal fatigue (5) In patients with chronic coughs especially winter coughs and gradually increasing dyspnea This symptom arouses suspicion more often in patients past forty (6) In any case of pleurisy with effusion and in patients who present any pulmonary symptoms or any of the vague constitutional disturbances and who give a history of pleurisy with effusion some time previously (7) In any case of spontaneous pneumothorax remembering that tuberculosis is one of the most common causes (8) In any patient who presents symptoms which may be due to tuberculosis outside the lungs since the original lesion most frequently is in the lungs This includes patients who come because of hoarseness which may be found due to tuberculous infection of the larynx or because of fistula in ano which sometimes is tuberculous It is depressing to see patients being treated for some extrathoracic tu

c ists of alveoli indicates a destructive necrotic process in the lung and this likewise is not of specific diagnostic value Since tuberculous ulceration may be a cause the important thing is to demonstrate tubercle bacilli The sputum sometimes may be found to contain blood clots in the form of bronchial casts after the patient has had a hemoptysis

Other Laboratory Tests — Examination of the *blood* as indicated previously has no specific value The demonstration of specific antibodies by the complement fixation test is evidence that the patient has been infected at some time with the tubercle bacillus but not necessarily that he is suffering from tuberculosis of clinical significance Further research may show that the antibody titer is of value for this purpose (Wadsworth) In acute phases of tuberculosis the leucocytes may be increased to 15 000 or more per cu mm with a predominance of polymorphonuclear neutrophil cells usually not more than seventy to eighty per cent beyond this the differential count may be of value in deciding the status of the lesion after the diagnosis has been made The count of erythrocytes and estimation of the hemoglobin in the early stages of tuberculosis show little or no abnormality

Later there are varying degrees of change indicating secondary anemia which becomes quite profound in some cases of generalized tuberculosis and in cases of pulmonary disease complicated by intestinal tuberculosis When secondary nutritional changes or amyloidosis develop characteristic alterations of the blood proteins may be demonstrated Appropriate tests may show an impairment of liver function Occasionally an interested and assiduous worker reports recovering tubercle bacilli from the blood of cases of terminal disease or acute generalized miliary tuberculosis but Loewenstein s claims of finding bacillemia frequently have been discredited (Wilson)

Examination of the urine as a rule reveals no significant change In febrile cases a small amount of albumin is found frequently and in the advanced stages severe albuminuria possibly with cylindruria may be due to amyloid degeneration of the kidneys In any pulmonary case as Jameson has emphasized the finding of a small amount of pus or small quantities of albumin with or without an increase of erythrocytes should arouse a suspicion of a renal tuberculous lesion

The *tuberculin test* usually is not of positive value and therefore need not be employed as a routine measure When the diagnosis is questionable it may be distinctly helpful if the patient fails to react The failure is particularly significant in patients who harbor demonstrable pulmonary lesions and who are not severely ill patients in the terminal stages of tuberculosis may not react except to very large doses

infiltration in either or both lungs supports the diagnosis of tuberculosis in young people and in many elders Careful history taking and a period of observation are the most important means of confirming the diagnosis in such cases when the bacteriological examination gives negative results When the examination reveals a pulmonary cavity associated with fresh or old fibroid infiltrations the diagnosis of tuberculosis is almost certain but the demonstration of tubercle bacilli is required The organisms certainly should be found in mucopurulent sputum if the patient produces any from the chest otherwise in the gastric contents

In any questionable case in which the diagnosis has not been settled by the finding of tubercle bacilli the discovery of extrapulmonary tuberculous lesion may be of decisive help If their origin and behavior is understood the clinician will be able to utilize the evidence to great advantage For example in the case of a questionable pulmonary lesion the finding of an infiltration at the posterior insertion of a vocal cord makes the diagnosis of tuberculosis almost certain Likewise the pattern of the pulmonary lesions particularly as this is revealed in the roentgenograph may suggest clearly the previous way of extension of the infection thus warranting a positive diagnosis Apical or subapical localization in one or both lungs with or without secondary lesions below is one of the prominent features of tuberculosis but confinement to a lower lobe is not rare With extremely few exceptions observation during a period of a few weeks or several months will settle the diagnosis not only of the nature of the lesions but also of their clinical significance

Diagnosis by Case Finding Surveys — The investigations of recent years have shown clearly that most patients will not seek medical advice until the disease in the lungs has passed into the more advanced stages At the start of the antituberculosis campaign it was thought that this situation could be corrected by making the lay public conscious of the early manifestations of the disease and by educating physicians to make the diagnosis promptly by physical examination Action based on these conceptions did not yield the hoped for results of an increase in the percentage of early diagnoses The reasons for this have become apparent in light of our increasing knowledge of the disease The early phases of pulmonary tuberculosis often are subclinical producing no symptoms or only the most obscure and vague type Our experience even with intelligent trained nurses has demonstrated that two thirds or more of those who become tuberculous are not conscious of symptoms requiring medical investigation until after a cavity has formed and the lesions have spread beyond the early infiltration This no doubt accounts for the facts that in New York City more than two thirds of patients entering clinics are

berculous lesion who have never had an examination of the chest This is inexcusable unless the physician is ignorant of the simplest principles of pathogenesis

A presumptive diagnosis of pulmonary tuberculosis is warranted in patients who present symptoms described in the preceding paragraph if roentgenographic examination shows a characteristic infiltration of the pulmonary parenchyma This is mentioned first because lesions of tuberculosis may escape detection by physical examination alone The probability of tuberculosis is increased by the roentgenographic appearance of a recent bronchopneumonic infiltration particularly if this is associated with rarefactions suggestive of cavity formation If in addition moist rales are detected on physical examination particularly in the upper half of the chest the presumption grows and is strengthened further by eliciting the signs of cavity with or without surrounding consolidation Pulmonary fibrosis is the end product of a number of conditions and the finding of this alone does not have the same weight however associated changes such as cavity or well defined calcification speak strongly for tuberculosis The discovery of a pleural effusion which is not clearly explained on other grounds warrants the presumption of tuberculosis The observation of bloody sputum strengthens the presumption under any of these conditions and may do so even though physical signs of significance are not elicited The value of these observations is relative and they are particularly significant in young people

A conclusive diagnosis of pulmonary tuberculosis is warranted when after demonstrating a lesion of the lung acidfast bacilli are discovered in the sputum The demonstration of non pathogenic acidfast bacilli is so rare that the possibility should not stand in the way of this conclusion It is to be emphasized again that tubercle bacilli may be demonstrated in cases in which the physical examination alone yields no definite findings the roentgenographic findings are almost always positive and usually include evidence of excavation The finding of tubercle bacilli in cases in which the roentgenograph is clear indicates a laboratory error which should be investigated or else that a tuberculous lesion is concealed beneath a dense structure like a rib or located outside the lung perhaps in the trachea or bronchus the latter is most unusual unless there is also a parenchymal lesion Pulmonary infiltrations demonstrable in the roentgenograph which increase or persist with little change for more than three or four weeks warrant a diagnosis of tuberculosis unless other findings arouse doubt this is true even when tubercle bacilli cannot be demonstrated and particularly in patients below the age of forty

The presence of pleurisy with effusion in association with a persistent

such as the poor usually are found to have higher rates of tuberculosis

So far as the practicing physician is concerned it may be said that routine fluoroscopy or other x ray examination of each of his patients would from time to time disclose lesions of previously unsuspected pulmonary tuberculosis and would contribute toward the thoroughness of his work and the solution of many clinical problems Having made a diagnosis of pulmonary tuberculosis the physician s obligation clearly is to urge the immediate examination of other members of the household Contacts are found to have a high incidence of tuberculosis particularly those in the immediate family circle At Bellevue Hospital Edith M Lincoln who is in charge of tuberculous children almost invariably has been able to discover a source of infection in the household or elsewhere shortly after finding tuberculosis in the young child It would be wise therefore as a part of routine health examinations for physicians to perform the tuberculin test upon all children and to seek out a possible active case in the family when the child reacts With a vision of these and similar possibilities for the prevention and control of the disease the physician may become an agent for great good in his community by advocating and promoting appropriate measures

Differential Diagnosis

Because of the wide prevalence of the infection tuberculosis must be considered often in differential diagnosis Few diseases present such a diversity of manifestations to simulate so many other conditions If one has a good comprehension of the pathogenesis of tuberculosis and the symptomatology of its various phases differential diagnosis may with few exceptions be carried promptly to a definite conclusion The conditions which are more commonly to be distinguished include those in which constitutional disturbances predominate and those in which respiratory symptoms are most prominent In the first group are to be considered fevers of obscure origin particularly when these persist for long periods of time such as melitensis bacterial endocarditis and tularemia Consideration of such possible origins and specific findings obtained from serology and blood cultures may settle the diagnosis quickly If tuberculosis is among the possibilities thorough physical and roentgenographic examination of the chest is most important Febrile pulmonary tuberculosis is on the basis of lesions which will be revealed by the roentgenograph if not by physical examination or the finding of tubercle bacilli in the sputum

found on the first visit to have advanced disease and that 85 per cent and more of the patients entering sanatoria are afflicted similarly This together with the revelation that many lesions are not detected by physical examination alone suggested the experiment of surveying large groups of the population with roentgenographs of the chests In a relatively short time a vast amount of information has been accumulated from this source Typical surveys such as those reported by the health departments of New York City and Detroit disclose tuberculosis in one to two per cent of the people the proportion increasing in older age groups In the experience of Fellows at the home office of the Metropolitan Life Insurance Company in New York the number of cases found annually did not decline appreciably between 1928 and 1938 which is in line with other observations that morbidity from tuberculosis has not declined in proportion to the mortality The other disclosure of great significance is that 75 to 90 per cent of the cases discovered are in the early and minimal stage of the disease this means of course that most of them may be treated with the promise of complete recovery and that only few of them will have developed cavities permitting them to spread the infection to others before discovery

These experiences have introduced a new note in the campaign for early diagnosis and have revived hope for the ultimate control of the disease in many communities As an instrumentality for discovering these cases some physicians have employed the fluoroscope or the paper film but all agree that except for its expense the celluloid acetate film is to be preferred In recent months devices have been perfected to permit photographing the fluoroscopic image of the chest on a miniature (35 mm) film or on a 4 × 5 film which may reduce costs greatly

In groups of people in which the expected incidence of tuberculous infection is low some have adopted the procedure of making tuberculin tests and procuring roentgenographs only of those subjects who react In many communities however it is just as economical to omit the tuberculin test an added advantage of the routine roentgenograph is the revelation of a certain number of previously unknown non tuberculous lesions Because of the lower incidence of clinically significant tuberculosis in childhood there is a growing tendency to confine case finding projects to adolescent youths and adults among these a greater number of active and potentially active and infectious cases will be found Groups in which surveys have proved to be especially advantageous are industrial employees high school and college students nurses pregnant women and the recipients of community funds for relief Such groups already more or less organized are more readily accessible for examination and some

ness may be attributed entirely to the tuberculosis and the diabetes may be overlooked

Conditions in which respiratory symptoms predominate are more often to be differentiated Bronchitis and sinusitis may raise the question because of chronic cough recurrent fever malaise and other symptoms of toxemia The characteristic history linking up upper and lower respiratory tract symptoms the clearness of the lungs on physical and x ray examination except perhaps for basal rales and rhonchi during acute attacks the failure to find tubercle bacilli in the sputum and the state of well being during favorable weather eliminate tuberculosis while proper examination of nose and sinuses usually discloses the seat of trouble

The acute pneumonias not infrequently have to be distinguished particularly if these are atypical in onset and course Acute pneumococcic pneumonia is not often confused and then only with acute pneumonic tuberculosis While the onset of the latter may seem to be very acute careful questioning usually will reveal prodromal symptoms such as a slight or moderate productive cough perhaps with some loss of weight of several months duration In acute tuberculosis it is rare to see herpes of the lips or prune juice sputum and there is a striking difference in the appearance of the patient In spite of high fever he usually does not have chills nor exhibit the same degree of cyanosis or grunting respiration as the pneumonia patient and often states that he does not feel very badly While physical and x ray examination both may reveal solidification of one or more lobes this is likely to be less complete in tuberculosis In the latter case showers of moist moderately coarse rales and a rarefied area as shown in the roentgenograph may be significant in the center of the solidification because of the suggestion of cavity Careful bacteriological study of the sputum is most important but one must remember that pneumococci particularly of the higher types may be found in the sputum of tuberculous patients and that repeated examinations may be necessary to reveal tubercle bacilli

There is a rather similar difference in the behavior of acute bronchopneumonia and the process of differentiation is very much the same The absence of a history of immediately preceding acute upper respiratory tract infection should be given some weight in favor of tuberculosis Bronchopneumonic tuberculosis except when it is of hematogenous origin practically always represents a dissemination of the infection from a pre existing cavity and this should be demonstrable at least by x ray examination and sooner or later by the finding of tubercle bacilli in the sputum In the hematogenous type the long course gradually increasing lesions and the uniform distribution throughout both lungs are the significant

As considered elsewhere gradually developing hematogenous forms of tuberculosis may be more obscure and the difficulty increases if the lungs are clear and only such abnormalities as an enlargement of the tracheo bronchial lymph nodes and possibly a pleural effusion are revealed In such cases one must be on the alert for the appearance of lesions else where in the body such as in the superficial lymphatics spleen peri toneum skin eyes etc and when one of these is easily accessible a biopsy may be indicated to settle the question A negative tuberculin test may be of value but is not to be relied upon absolutely for differen tiation especially in highly febrile cases Examination of serous fluid or pus from the pleura or other collection may reveal the presence of tubercle bacilli or perhaps some non tuberculous organisms or specific reaction of diagnostic significance

In other cases especially in older people consideration of tuberculosis is indicated because of a gradual afebrile wasting and a distinction may have to be made from malignant disease The finding of fibrous pul monary scars may complicate the picture because of their uncertain clin ical significance In still others even though the lungs are clear or harbor apparently healed lesions the possibility of other foci such as tuberculosis of the intestine may be suspected The finding of a mass in the right lower quadrant occasionally raises the question of hyperplastic tuber culosis or malignant disease A painstaking examination and a period of observation may be necessary and in some cases exploratory laparot omy Reasoning on the basis of pathogenesis it may be said for exam ple that tuberculosis of the intestine is seldom found except where there has been a previous ulcerating pulmonary tuberculosis and the latter should be demonstrable by suitable examination In the case of healed or healing pulmonary lesions progressive wasting is not to be expected unless there is some other tuberculous focus failure to demonstrate the latter necessitates further search for a non tuberculous cause

Hyperthyroidism may simulate tuberculosis because of the progressive loss of weight fatigue nervousness and low fever As a rule tuberculosis is ruled out readily by physical and x ray examination of the chest Fe brile tuberculosis causing elevation of the metabolic rate usually is pro gressive and readily identified by proper examination Tuberculous patients may be nervous and irritable but as a rule less so than hyper thyroid patients the former rarely manifest the triad of marked tremor exophthalmus and goiter Diabetes mellitus should be confused rarely and then only if there is a complicating pulmonary tuberculosis to which these patients are liable Unless the history examination and interpretation of the findings are thorough and reliable the loss of weight and weak

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points Mild bronchopneumonias particularly localized in the upper half of one lung may be confusing at the start since the slightness of the symptoms and physical findings and the patch of mottling in the roentgenograph admit the possibility of tuberculosis In most cases there is a history of definite and rather protracted acute upper respiratory tract infection Râles if any often are distributed beyond the limits of the lesion visualized by x ray whereas in tuberculosis usually they are fewer smaller and definitely limited The behavior under observation is most important since bronchopneumonic lesions usually show a definite tendency to resolve within a few days or a week while tuberculous lesions change much more slowly if at all Here again the failure to demonstrate a cavity which would be the source of a bronchopneumonic spread of tuberculosis is most significant Serous pleural effusion in the presence of non tuberculous pneumonia may cloud the picture further the determining factor usually being the rapid absorption of both pulmonary and pleural exudates tuberculous pleural effusions are absorbed slowly but the pulmonary lesions are left behind The blood leucocyte count always is useful since in acute tuberculosis this usually does not rise above 12 000 or 15 000 per cu mm and rarely above 20 000 while the polymorphonuclear neutrophil ratio rarely rises to 90 per cent and usually remains between 70 and 80 per cent

Lung abscess usually is distinguished by the clinical onset and course The history of a preceding operation possible aspiration of foreign body drunkenness or other unconsciousness permitting aspiration of material from the mouth or pharynx is significant Non putrid abscesses most often are metastatic from some preexisting focus such as osteomyelitis Putrid abscesses and gangrene usually are due to suppurative pneumonia following the aspiration of septic matter from the mouth the source frequently being peridental pockets of pyorrhea The sudden onset possibly following a cold with acute pain in the side, fever and within a few days the production of copious quantities of foul purulent sputum which settles in three layers suggests the diagnosis Physical examination may not be very helpful in differentiation but the roentgenograph usually shows a cavity with surrounding homogeneous pneumonic reaction differing from the mottling of tuberculosis and an enclosed fluid level this may be situated anywhere in the chest oftener in the upper half Failure to demonstrate tubercle bacilli is most significant and the blood count is helpful Chronic abscesses with organized walls present physical and x ray signs which may duplicate those of tuberculosis The history of the onset and preceding clinical course and the failure to find tubercle bacilli are the significant distinctions

Bronchiectasis must be considered because of the frequent history of chronic cough blood spitting and febrile episodes The common origin with bronchopneumonia in childhood and subsequent pneumonic episodes without permanent and serious impairment of the general health are distinguishing features While the lesions may be apical usually they are basal giving rise to rales and perhaps other signs the roentgenograph seldom shows a definite cavity but only a varying accentuation of the pulmonary markings perhaps with surrounding densities of pneumonia or fibrosis Failing to find tubercle bacilli in the sputum which may be scanty or copious purulent putrid or bloody the diagnosis is made finally by the bronchogram after introducing iodized oil into the affected regions

Cancer of the bronchus must be distinguished after the age of forty sometimes earlier Since the symptoms may be those of loss of weight cough and expectoration of pus and blood the history may not be very helpful unless there is persistent pain in the chest Physical and x ray findings are most useful since in bronchial carcinoma there may be a uni lateral wheeze or rhonchus and usually a diminution of breath sounds in the contiguous lobe or lobes Parenchymal rales may be relatively scarce in comparison with the roentgenographic shadow which consists of diffuse or localized densities frequently confined strictly to one lobe and having a ground glass homogeneous character different from the mottling of tuberculosis Lymph nodes enlarged by metastatic invasion may be indicated by a widening of the hilar and mediastinal shadows Paren chymal cavities seldom appear until late in the disease when progressive suppurative pneumonia is responsible for this as well as for the increasing quantities of purulent sometimes foul sputum in which tubercle bacilli are not found Bronchoscopy or the biopsy of an accessible supracla vicular node may settle the diagnosis occasionally cancer cells can be demonstrated in the sputum

Special mention may be made of apical tumors to which Pancoast and others have directed attention and which may simulate tuberculosis particularly because of their location These so called superior sulcus tumors most often seem to be due to carcinoma starting in a small or terminal bronchus near the pulmonary apex and extending outward to involve the pleura and the brachial plexus Prominent findings are the absence of pulmonary cavity the homogeneous character of the pul monary density the pain and wasting in the shoulder and arm Horner s syndrome and invasion and destruction of the upper ribs on the affected side

Metastatic tumors in the lung or in the tracheobronchial lymph nodes particularly when associated with a pleural effusion may have to be dis

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also the development of pleural effusion Sometimes confusion also occurs in cases in which indurative changes have developed in the lungs from prolonged or recurrent congestion Differentiation seldom is difficult since a thorough examination usually reveals evidence of a cardiac lesion and other findings may demonstrate complicating septicemia pulmonary congestion or infarction Furthermore physical and x ray examination show no destructive changes in the lungs as would be found in tuberculosis sufficient to cause cough and expectoration of mucopurulent sputum and blood

Silicosis and pulmonary fibroses of other origins sometimes suggest the possibility of tuberculosis and this in fact may be an associated condition In uncomplicated silicosis the occupational history the good general health the signs of emphysema without rales or only a few at the base of the lungs the absence of excavation and the demonstration by x ray of the characteristic nodular shadows make the diagnosis Other types of fibrosis are due most often to chronic non tuberculous infections often associated with chronic paranasal sinusitis Tuberculosis is eliminated on the basis of the history the absence of tubercle bacilli in the sputum and the rather familiar roentgenographic pattern of the lesions which may be associated with bronchiectasis

Emphysema may require particular investigation because the greatly distended air spaces may obscure underlying tuberculous lesions These in fact may be the cause of the emphysema in chronic fibroid cases and in certain cases of hematogenous origin in which there has never been any cavity formation but rather an arrest of the tuberculosis with a gradual proliferation of interstitial fibrosis In these cases a prominent symptom is dyspnea which sometimes may simulate chronic asthma Roentgenographically the picture sometimes is confusing when there is extensive bullous emphysema giving rise to thin walled clear round or ovoid rarefactions varying in size from a small honeycombed area to an enormous space simulating pneumothorax

Other conditions to be distinguished include chronic infectious processes in various stages of suppuration resolution and organization these occasionally represent secondary extensions from adjacent structures such as the pleura or the subphrenic regions Such a lesion may be the result of a chronic empyema possibly with bronchopleural fistula or a subphrenic abscess which has perforated the diaphragm and the basal pleura The history is most important in distinguishing such odd lesions Chronic organizing pneumonia sometimes is caused by the repeated or prolonged aspiration of oil food or other substances Examples include so called oil pneumonia or lipoid pneumonia in sickly children who have

tinguished Prominent features of value include mildness of the fever if any in proportion to the progression of the lesions the paucity or absence of pulmonary râles the absence of excavation the prominence of dyspnea as the lesions become widespread and the continued recurrence of the pleural effusion which may be clear or bloody both in tuberculosis and in malignant disease A positive diagnosis is made by finding the source other metastases or malignant cells in the sediment of the pleural fluid Bronchoscopy is a rule is not of value

Other tumors in the thorax which may have to be distinguished include aneurysm of the aorta cysts and lymphoblastomas particularly when there is pressure upon or invasion or irritation of the bronchus in which case there may be an associated mild or acute suppurative pneumonia Tuberculous adenopathy of the mediastinum or infiltration of pulmonary parenchyma may have to be distinguished In addition to a study of clinical features to discover such clues as the Pel Epstein fever of Hodgkins disease a syphilitic basis for aneurysm or referred pains from the pressure of growing tumors the investigation may include such measures as a biopsy of accessible lesions and the use of artificial pneumothorax to permit a different visualization of the masses in question Tuberculosis may be excluded finally by failing to discover the evidence described above and a negative tuberculin test may be of great value

Fungus infections of the lung are relatively rare but when present give rise to pneumonic or chronic granulomatous lesions which may simulate tuberculosis because of their gradually infiltrating character tendency to fibrosis and occasionally to suppuration and excavation The responsible fungi include *Actinomyces Streptothrix Blastomyces Aspergillus Torula* and *Coccidioides* In rare cases other organisms may be involved Differential diagnosis rests mainly on the failure to find tubercle bacilli clinical features which may include the history of a portal of entry in a lesion of the skin or mouth the involvement of various structures by blood stream dissemination or by direct extension as through the chest wall the opportunity of exposure to infection as in the handling of grain or the inhalation of desert dust (coccidioides) the demonstration of granulomatous lesions serological and hypersensitivity skin tests and microscopic demonstration of the fungus in great numbers in the sputum its cultivation on suitable media and animal inoculation The common mistake is not in overlooking fungus infection but in overlooking tuberculosis especially when a few fungi which were saprophytic in the mouth are demonstrated in the sputum

In cases of heart disease tuberculosis occasionally may come into question because of mildly febrile episodes blood spitting and cough

ment at once remembering that the management in the early weeks has a definite influence on the ultimate prognosis

Small latent lesions discovered in older people require longer study to estimate their significance Identification of an old primary complex which appears calcified in a person past twenty seems to have little prognostic significance and extensions directly from these lesions seldom occur treatment is not required Fibroid scars of slight or moderate extent in people past thirty usually do not indicate treatment since under good living conditions they are not likely to break down Periodic examination however is indicated to observe whether or not they remain stable In people of this age group lesions of uncertain healing and stability may have to be watched for some weeks or months in order to determine the therapeutic needs During observation the patient sometimes may be allowed to continue his daily activities or to limit them according to the indications Roentgenographs of the chest made at monthly intervals estimation of the erythrocyte sedimentation rate at intervals of a week or so and a similar study of the differential blood count recording of the temperature and pulse at four hourly intervals throughout the day for one or a few weeks the body weight curve and other symptoms usually enable one to decide whether the margin of safety is sufficient without a period of rest treatment Such observations are particularly useful when the character of the pulmonary lesions is indeterminate between an active inflammation and a beginning fibrosis

Any changing lesion as shown in serial roentgenographs is to be considered unstable and threatening whether this change be progressive or recessive the latter of course indicates a favorable trend An ulcerative lesion revealed by physical or x ray examinations or the finding of tubercle bacilli in the sputum always impairs the prognosis because it may be a source of bronchogenic dissemination Stabilized and isolated fibroid cavities may cause no symptoms except for cough and such tests as the erythrocyte sedimentation rate may be within normal limits but the potential threat to health and life cannot be denied

In the cases of more obvious and extensive pulmonary tuberculosis with clinical symptoms indications for treatment usually are more clear cut and the prognosis less favorable The extent of lesions alone is of prognostic import For example the follow up of patients treated at the Trudeau Sanatorium between 1916 and 1938 shows that death has occurred in 8 66 per cent of the minimal cases 21 04 per cent of the moderately advanced and 56 39 per cent of the far advanced These figures represent an unusually good experience because of the careful selection of patients who were under treatment in this sanatorium The

received nose drops mineral oil cod liver oil or cream and aspirational pneumonia observed in patients with nervous lesions interfering with deglutition and in patients with cardiospasm and esophagitis or with diverticula or fistula of the esophagus

Classification

There have been numerous classifications of pulmonary tuberculosis most of which are based mainly on the anatomical extent of the lesions The classification used generally in America is that of the National Tuberculosis Association published in its booklet , Diagnostic Standards This is comprehensive and includes not only a grouping of cases according to the various features of the lesions but also according to symptoms and other data As to extent of lesions cases may be classified as minimal moderately advanced or far advanced The results of treatment or observation may be classified further as quiescent apparently arrested arrested apparently cured unstable (active) or died

Prognosis

Diagnosis must take into consideration after determining the presence of tuberculous disease an estimate of the type extent and character of the lesions the threat to the patient s life and health and the need for and the probable response to treatment The appraisal is made on the basis of the diagnostic examinations which have been outlined and proper correlation of the findings It is logical to consider basically the extent and morphological character of the lesions and then their functional and other effects One must include not only patients who present themselves because of symptoms but also many others whose disease is detected in case finding surveys The factors of age race and living conditions must be given consideration Pulmonary infiltrations even slight identified in adolescent youths and young adults are notoriously unstable and in great danger of progressing particularly in young girls and boys and more particularly in negroes The mere diagnosis in these cases is an indication for treatment since without this a majority probably will go on to advanced tuberculosis Even under rest treatment progression sometimes may occur according to Braeuning in as many as 5 per cent but this will be detected early and some appropriate form of collapse therapy then may be applied

Because of the potential hazards one should not wait to determine whether or not the lesions are active but should advise rigid rest treat

effects on living tissues the resistance of the tubercle bacillus and the relatively avascular character of many of the lesions Recourse is had therefore to the natural resistance of the human host constantly evidenced by the low morbidity and mortality in relation to the general prevalence of the infection Just as impairment of the natural resistance may be caused by undernutrition fatigue complicating disease and occupational hazards experience shows that reverse influences have the opposite effect and promote healing of lesions Specific mechanisms are hard to identify Empirically it has been learned that the promotion of normal physiological functions such as digestion and circulation is favorable that relaxation and rest are good influences partly because of the decreased respiratory motion and the slowing of the circulation that a properly balanced ration favors healing processes that mechanisms like capillary permeability may affect the lesions favorably or unfavorably as indicated by variations during menstruation or under the influence of such agents as tuberculin and that if time is allowed for adequate fibrous encapsulation of lesions progression of the disease may be arrested permanently

Rest — The general plan of treatment therefore rests on the recognition and wise application of such principles The first fundamental is *rest* and the degree of this varies according to indications In the case of any unstable lesion or of a patient who has been discovered first to be in the need of treatment absolute bed rest is indicated for a time The patient is not allowed bathroom privileges and when there are very active symptoms is not even permitted to feed himself He should lie flat in bed for most of the twenty four hours changing his position for comfort Bed baths are given Sometimes it is helpful if the patient favors a certain position in bed In the case of a unilateral lesion he should be encouraged to lie on the affected side since this will inhibit respiratory motion and provide some added local rest cylindrical bags of sand or bran may be used for support and comfort A bag of lead shot weighing from two to five pounds sometimes is placed upon the affected side while the patient is lying recumbent this may inhibit motion slightly and induce the patient to keep quiet The bag may be made of two pieces of canvas or other durable cloth each about six inches square stitched together at the edges Before closing one side cylindrical compartments are made by running five or six lines of stitches about an inch apart through the bag and into these compartments the shot are poured and the bag closed Thus the shot are prevented from shifting Various splints and binders have been used on one side of the chest for such purposes but the discomfort usually interferes too much How long

prognosis of course is infinitely better in those who responded well to sanatorium treatment death occurring in only 0 31 per cent of the minimal cases discharged from Trudeau as apparently arrested Likewise the character of the lesions has an important bearing on prognosis productive and fibroid lesions promising a much better prospect for the patient than exudative and caseous ones The association of cavity with these represents an additional threat which varies according to the character of the surrounding lesion the cavity with sloughing caseous walls is of particularly bad omen

The acuteness of exudative caseous lesions as well as their extent is of great importance In most cases of moderately or far advanced acute pneumonic or bronchopneumonic tuberculosis further spread of the disease occurs and this may be extremely rapid resulting in death within six or eight weeks phthisis florida In other cases progress of the disease may be slowed or interrupted so that the patient may live from one to five years during most of which time he may have mild moderate or intermittent symptoms of active disease In a minority stabilization eventually occurs and finally remarkable healing so that cavities may be closed and the sputum may become negative for tubercle bacilli Such patients usually have a permanent handicap on account of necessary limitation of their activities the possibility of relapse and functional impairment due to the fibrosis and secondary emphysema If a complication such as severe laryngeal tuberculosis dominates the picture the prognosis is altered accordingly and death may occur much earlier

Since tuberculosis usually is not diagnosed until it has entered an advanced stage the general prognostic picture is not a very happy one About fifty per cent of sanatorium patients relapse after leaving the institution and the average duration of life after diagnosis is only about five years

Treatment of Pulmonary Tuberculosis

The principles of treatment are simple although the numerous modifications and adjuvants require experience and seasoned judgment if the patient is to derive the greatest benefit Up to the present no direct means of attack has been available Numerous chemotherapeutic agents have been tried particularly when they have been found to exert an inhibiting or lethal effect upon tubercle bacilli growing in the test tube or when they have shown the capacity to modify the course of the disease in experimental animals None of these however has been proved yet to influence human tuberculosis decisively largely because of their toxic

effects on living tissues the resistance of the tubercle bacillus and the relatively avascular character of many of the lesions Recourse is had therefore to the natural resistance of the human host constantly evidenced by the low morbidity and mortality in relation to the general prevalence of the infection Just as impairment of the natural resistance may be caused by undernutrition fatigue complicating disease and occupational hazard experience shows that reverse influences have the opposite effect and promote healing of lesions Specific mechanisms are hard to identify Empirically it has been learned that the promotion of normal physiological functions such as digestion and circulation is favorable that relaxation and rest are good influences partly because of the decreased respiratory motion and the slowing of the circulation that a properly balanced ration favors healing processes that mechanisms like capillary permeability may affect the lesions favorably or unfavorably as indicated by variations during menstruation or under the influence of such agents as tuberculin and that if time is allowed for adequate fibrous encapsulation of lesions progression of the disease may be arrested permanently

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rest should be continued varies greatly in the individual case and according to the philosophy and foresight of the physician

Rest in Bed — Rest in bed is continued until all symptoms of constitutional toxemia have subsided until the lesions have reached a point of well established healing and stability as indicated by the routine examination of the sputum for tubercle bacilli and the roentgenographs until significant complications have been brought under control, and until sufficient time has elapsed to promise continuation of the favorable trend Often it is prolonged for some months or weeks after all active symptoms such as fever have subsided and in certain cases like young people with early infiltrations rest in bed may be advisable for as long as six months to a year even though the patient has never had serious constitutional symptoms The reason is that adequate healing in this early stage offers the prospect of saving the patient from the prolonged disability of advanced tuberculosis and early death Early compromises are justified in certain cases of advanced fibroid tuberculosis in which complete recovery cannot be anticipated and the patient is being deprived of his comfort and happiness but otherwise relaxation of restriction is permissible only seldom Reluctantly one sometimes is obliged to compromise with the patient who is nervous and whose emotional instability defeats the purpose of rest in bed

Return to Activity — Stability having been established after weeks months or years as the case may be the patient is allowed gradually to undertake activity starting with sitting up in bed bathroom privileges and later a short walk about the room As a rule a few weeks or months pass before he is permitted to walk more than a half an hour once or twice a day greater caution being used with young people who have developed lesions recently During the intervals between exercising the patient lies on his bed or in a comfortable chair and may read write or engage in light occupations such as knitting weaving typewriting leather tooling etc It is desirable always to advise an afternoon nap of an hour or so and at least ten hours of sleep at night The duration of this scheme of treatment varies In most of the recently developed cases two years of careful living are necessary after quiescence of the disease has been established to insure durable healing during the latter part of this time the patient may have been undertaking some light work but only under medical advice and observation In cases with fibroid or partially fibroid lesions the treatment frequently may be of shorter duration depending on the extent of the lesions and the response

Nursing — One of the most important requirements in the stages of active treatment is proper nursing The nurse being a rather constant

companion has great influence on the patient's progress and she should be selected for her experience, personality and attitude. Unless she has a comprehension of the behavior of the disease and the reasons for various procedures, her impatience and irritation will be imparted to the patient to his great detriment. On the contrary, her understanding, calm and cooperation will do much to further his ultimate recovery, particularly if she has the intelligence to divert him from excessive consideration of his disability to constructive thinking along other lines. The attitude of the physician likewise is vital and it is one of his functions to secure the complete confidence of the patient by explaining in an encouraging way the reasons for each step and particularly for the time required. It is often equally important to explain matters fully and repeatedly to the family, who otherwise may misunderstand the treatment and mislead the patient. The psychological and social environment has a definite influence on the course of events.

Guides to Response to Treatment. — This brings to attention the essential guides which are used to determine the response to any form of treatment, and these should be adopted always. The rectal temperature and the pulse rate are recorded and charted every four hours, and it is desirable also to record the respiratory rate, at least on certain days according to the indications. The body weight is recorded every two weeks unless the patient is too sick. A daily record is kept of the symptoms, particular note being made of pain, sweating or hemoptysis. Likewise the functions are watched, including the appetite, digestion and evacuations. Sputum is collected in a sanitary cup, disposable by burning, so that the quantity and character may be judged from day to day. The frequency of cough is noted. The patient's mental attitude, his ease of relaxation and his hours of rest and sleep are observed. Periodical physical examination is carried out at intervals indicated by symptoms, the nature of the lesions and the possible development of complication; in many sanatoria the routine is at least once monthly. Roentgenographs of the chest made at intervals are very important and if necessary these may be exposed with the patient in bed, preferably sitting, otherwise lying prone on the cassette. In cases with recently developed lesions or acute symptoms roentgenographs taken at weekly intervals for a time are valuable, while under more stabilized conditions once a month may be sufficient. With the development of acute exacerbations careful physical and possibly fluoroscopic as well as roentgenographic examinations should be made. These may be supplemented with blood counts, estimations of the erythrocyte sedimentation rate and other indicated procedures. Such careful observation usually will detect significant

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Nursing — One of the most important requirements in the stages of active treatment is proper nursing The nurse being a rather constant

of the family. He should have no intimate contact with any of the family, and young children should be kept from the room.

Diet.—The diet should be varied, well prepared and balanced in essential elements including vitamins. Overfeeding is unwise; the patient should be guided by his tolerance, taking small intermediate feedings of milk or some other light article if his digestion permits. If needed, extra vitamins may be provided in the form of fruit juice or in concentrated preparations. As a rule the diet can be adjusted so as to overcome any tendency toward constipation, and habits which previously were irregular may be corrected now.

Drugs.—No drugs are required except for symptomatic needs. Administration of calcium has not been demonstrated to be of particular value, except during the late stages of the disease; there is an adequate supply in the tissues with an ordinary diet. The administration of gold salts in the form of sanocrysin, gold sodium thiosulphate or some other combination still finds favor with some physicians, but there has been no proof of specific effect as first assumed. Amberson, McMahon and Pinner studied this drug in 1926 and were not able to determine any benefit from its use in tuberculous patients; harmful toxic effects were observed.

The newly developed sulfanilamide, sulfapyridine and dodecanoyl sulphanilamide and related derivatives have raised the question of their efficacy in tuberculosis. Rich and Follis, Buttle and Parish, Steinbach and Dillon, Feldman and Hinshaw, Climenko and others have conducted animal experiments; some got negative results, while others have observed a kind of inhibiting effect upon tuberculosis in animals. There is as yet no evidence of benefit obtained in human subjects. A short trial of sulfapyridine by Allison and Myers in my service at Bellevue Hospital showed no immediately favorable clinical effects. Further studies no doubt will be pursued in many clinics.

Tuberculin injections no longer are used by many physicians for treatment. Some still try it in fibroid indolent lesions which fail to heal completely, believing that the stimulation of a slight inflammatory reaction about the focus promotes healing. This effect cannot be denied in some cases, but the possibility of harm through over-stimulation must be recognized; observation for long periods of time of cases so treated leaves a dubious impression about the ultimate effect.

Heliotherapy, using natural sun or artificial mercury vapor or carbon arc lights, is not to be advised during the early stages of a pulmonary lesion of exudative character or in any progressive case. After the lesions have become well stabilized or fibroid, the tonic effect of mild, slowly in-

changes promptly and often will indicate the prompt use of special measures of treatment to prevent the disease getting beyond control It cannot be emphasized too strongly that dependence should not be placed solely upon symptoms in judging the effects of treatment Many lesions progress gradually without causing fever A patient not infrequently gains weight and looks greatly improved, even though a cavity is growing larger in the lung and complications sometimes develop without definitive early indications *Constant alertness and routine periodic observation* therefore, are prerequisites

Place of Treatment — The place where treatment is to be given is determined not only by medical indications but also by social and economic conditions The influence of climate is not as great as formerly supposed but in many cases is helpful The invigorating and tonic effect of cool clear mountain air and scenery especially on younger people should not be underestimated Likewise a patient either young or old may be able to relax and rest better in a climate which is warm dry and balmy than in one which is cold and humid High altitude in itself does not seem to offer significant benefit but is not a disadvantage except in fibroid cases in which dyspnea is a factor

As tuberculosis is encountered in practice possible benefits of climate often have to be sacrificed because of economic or other considerations which may be much more important The poor man usually runs into disaster if he borrows a few dollars to go to a favorable climate where in time he becomes a most unwelcome dependent on the charity of the community It is much better for him to remain near home where his social condition is better understood where he may see his family frequently and where he may apply for public benefits in case of great need Whether the patient should be in a sanatorium hospital or at home is largely a matter of convenience and individual conditions The institution has the advantage of an organized medical staff constant medical and nursing supervision facilities for every needed treatment and if properly conducted an atmosphere which promotes the necessary rest A stay in such place may afford an education which the patient sorely needs if he is to avoid relapse of the disease later However a poorly run and incompetently manned sanatorium is not a benison but a bane An important function of an institution particularly in the case of the ignorant or uncooperative patient is segregation to avoid infection of others A fortunately situated patient may stay at home and treatment may be carried out adequately and successfully there He should have a separate quiet room and strict supervision should be exercised to insure separation of him and his clothing utensils and equipment from the rest

of the family He should have no intimate contact with any of the family and young children should be kept from the room

Diet — The diet should be varied well prepared and balanced in essential elements including vitamins Overfeeding is unwise the patient should be guided by his tolerance taking small intermediate feedings of milk or some other light article if his digestion permits If needed extra vitamins may be provided in the form of fruit juice or in concentrated preparations As a rule the diet can be adjusted so as to overcome any tendency toward constipation and habits which previously were irregular may be corrected now

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creasing heliotherapy may be beneficial There seems to be no reason to cover the chest since the effects are general, but it must be remembered that overexposure anywhere sufficient to cause severe erythema may stimulate the lesions to unfavorable activity Exposure merely to cool moving air has a tonic effect and may be grateful to some particularly young people

Pneumothorax and Surgery —Artificial pneumothorax and surgical treatment of pulmonary tuberculosis is being practiced on an increasing scale The principle of these treatments is by relaxation of the elastic tension and by mechanical collapse of the lung to lessen respiratory motion to release tensions which interfere with the contraction of fibrous tissue to slow the pulmonary circulation of blood and lymph and to approximate the walls of cavities If attained these effects result in a lessening of the diffusion of toxins from the lesions with commensurate abatement of constitutional symptoms diminution of the active inflammatory processes a slightly increased rate of fibrosis diminution of discharges from cavities with the resultant prevention or lessening of bronchogenic dissemination and possibly the healing of cavitary defects which otherwise could not have occurred Approximated cavity walls sometimes may become bridged across and organized with fibrous tissue but if not the surrounding fibrous encapsulation may leave only a slit like defect The measures to create these effects are many and are used in varying combinations

Unfortunately the erroneous impression sometimes prevails that collapse therapy offers a convenient short cut to the solution of the tuberculosis problem My own experience in private sanatorium public hospital and clinic practice indicates that the results are greatly superior if the patient and the physician do not look upon this as a substitute but accept the principle that the healing of tuberculosis at best is a slow process and that the sacrifice of time is eminently justified by the ultimate advantages There is a great temptation to accept collapse therapy as an immediate expedient when in fact such use may involve heavier sacrifices in after years I am convinced of the soundness of the dictum that ultimate recovery under rest treatment alone if this is possible is better than recovery with the aid of collapse therapy which carries its own hazards and disadvantages In principle therefore collapse therapy of some sort is to be considered in cases in which a sufficient and reasonable trial of proper rest treatment has not accomplished the desired result or in cases in which upon diagnosis the disease has already made inroads of such extent that rest treatment alone does not promise much The measures employed include artificial intrapleural pneumothorax pa

ralysis of the diaphragm by phrenic nerve crushing or other interruption pneumoperitoneum extrapleural plombage or pneumothorax and thoracoplasty

Artificial pneumothorax is selected chiefly for those patients who have active and progressive lesions with excavation in one lung or lesions which are not likely to respond to rest treatment alone The opposite lung preferably should be clear or show only small localized non progressive lesions More extensive lesions are not necessarily accepted as a contraindication and in some cases attempts are made to collapse both lungs simultaneously or successively the results however are not as good as in unilateral cases The lung is kept collapsed by refills of air or other gas given at intervals of a few days to several months The pneumothorax is maintained as a rule for eighteen months to three or four years occasionally longer in order to allow adequate healing after which reexpansion is attempted by reducing the insufflations of air If the visceral pleura has not become fibrosed reexpansion may be effected except in the diseased sections of the lung and its function may be resumed the cavities remaining closed and the sputum negative for tubercle bacilli Under ideal conditions good ultimate results are obtained in fully one third of the cases attempted Among the other two thirds pleural adhesions may prevent an adequate collapse of the lung in this event the pneumothorax should be discontinued unless the adhesions can be severed by the operation of Jacobeus known as *intrapleural pneumonolysis*

Tuberculosis of the pleura is a frequent complication of artificial pneumothorax and effusions are observed in a great majority of cases These usually are serous but become empyematous in 5 to 10 per cent Healing of the pleural inflammation may lead to fibrosis preventing much reexpansion of the lung and possibly necessitating thoracoplasty later Ulceration of the pleura with development of a bronchopleural fistula is an occasional complication observed most frequently in cases of caseous tuberculosis Other complications such as air embolism during the introduction of air into the pleura are very infrequent

The question of using artificial pneumothorax in acute tuberculous pneumonia particularly in negroes often comes up Occasionally a good result is observed but in general the response is discouraging Artificial pneumothorax frequently is used to control hemorrhage which otherwise is intractable Decision to use the procedure in any case involves a consideration of the hazards and possible benefits with and without it pleural complications being the most serious disadvantages of this treatment

Paralysis of the diaphragm on one side has its most striking effect in partially stabilized cases in which there is a rather isolated thin walled

cavity not adherent to the pleura and not surrounded by much tuberculous infiltration Relaxation of the surrounding elastic structures may promote healing Early enthusiasm for this operation encouraged by the technical ease with which it may be done has subsided greatly in recent years because of its frequent ineffectiveness Some use it for the early tuberculous infiltration but since these patients need bed rest the advantage is doubtful The procedure is quite futile and may waste valuable time in cases of extensive or fibrous tuberculosis It may produce circulatory disturbances and may be a positive disadvantage when thoracoplasty has to be performed later

Artificial pneumoperitoneum to elevate and inhibit the motions of the diaphragm is practiced in some institutions when other measures are unsuccessful but there does not seem to be much to commend it in the minds of most physicians It may cause considerable discomfort to the patient and the irritation of the peritoneum by the air may lead to fibrous thickening (Trimble and others)

Extrapleural stripping of the parietal pleura from the thoracic wall overlying a pulmonary tuberculous lesion has been attempted by many entry being gained by resecting one or two ribs usually in the upper interscapular region Fat paraffin muscle and other substances have been introduced into the resulting extrapleural space to keep the diseased part of the lung collapsed but these have the disadvantage of sloughing through the chest wall or into the lung in some cases In recent years air has been used to preserve the space as in the case of intrapleural pneumothorax the newer procedure therefore goes by the name *extrapleural pneumothorax* The chief use of this treatment is to attempt to bring under control unstable lesions which cannot be so influenced in other ways the prospect is that many or perhaps all of these patients eventually will need a thoracoplastic operation Pyogenic or tuberculous infections sometimes occur in the extrapleural space and there may be a chronic serous hemorrhagic or purulent effusion Observation of these cases has not yet been sufficient to permit a final appraisal of the procedure

Thoracoplasty is carried out by an extra pleural resection of the ribs over the affected part of the lung so as to release the attachments and tensions which may be preventing the closure of cavities and to exert positive compression to accelerate this process There are various modifications of the operation designed by the surgeon according to the distribution and character of the pulmonary lesions The most suitable type of case is that of the young patient in good general condition with no complications but with a chronic fibroid tuberculosis of one lung in which there is a small or moderate sized cavity unresponsive to rest and

artificial pneumothorax treatment The operative risk in the hands of skilled surgeons is less than 5 per cent and the prospects of a satisfactory result including closure of the cavity and a negative sputum are excellent 70 to 90 per cent of the selected cases Thoracoplasty is performed under many other conditions where the need is pressing but the prospects of good effects are not as promising The operation is not used in acute or rapidly progressive cases and is less effective when there is no existing tendency toward fibrosis Here as with other collapse procedures the rest cure is advised for a year or so after the operation in order to gain the maximum benefit from a drastic step Bilateral thoracoplasty has been performed sometimes but its field is very limited The unilateral operation undoubtedly offers to many who otherwise would be chronic invalids the prospect of restitution to a useful and comfortable life not to speak of the elimination of sources of infection

Surgical treatment of pulmonary tuberculosis is discussed also in Chapter XII-A which follows this chapter

Treatment of Symptoms

Cough and Expectoration —These symptoms are traceable most often to discharging cavities in the lung and occasionally to tuberculous changes in the trachea and bronchi or to tuberculous laryngitis General rest treatment by lessening the movement of the lungs and pulmonary circulation often is sufficient for control So long as cavities exist it is important of course that these be drained adequately and a certain amount of expectoration therefore is essential It is accomplished usually in the morning upon awakening or following breakfast During the remainder of the day there may be only occasional expectoration and the patient usually notices that the amount is influenced by his activity and by his indulgence in talking laughing or other respiratory exercise By contrast a cooperative patient upon proper instruction will be able materially to control the symptom He is taught not to cough at each bronchial or laryngeal stimulus but to await patiently the accumulation of discharges which slowly rise into the larynx and then may be expelled with minimum of cough or mere clearing of the throat In cautioning against the swallowing of infectious discharges which of course is important the patient should not be so frightened that he keeps coughing unnecessarily thereby moving the lungs too frequently and irritating the passages Many patients are able by conscious control to raise two or three ounces of sputum daily with relatively few coughs

In case the patient keeps coughing and expectorating in spite of the

cavity not adherent to the pleura and not surrounded by much tuberculous infiltration. Relaxation of the surrounding elastic structures may promote healing. Early enthusiasm for this operation, encouraged by the technical ease with which it may be done, has subsided greatly in recent years because of its frequent ineffectiveness. Some use it for the early tuberculous infiltration, but since these patients need bed rest the advantage is doubtful. The procedure is quite futile and may waste valuable time in cases of extensive or fibrous tuberculosis. It may produce circulatory disturbances and may be a positive disadvantage when thoracoplasty has to be performed later.

Artificial pneumoperitoneum to elevate and inhibit the motions of the diaphragm is practiced in some institutions when other measures are unsuccessful, but there does not seem to be much to commend it in the minds of most physicians. It may cause considerable discomfort to the patient, and the irritation of the peritoneum by the air may lead to fibrous thickening (Trimble and others).

Extrapleural stripping of the parietal pleura from the thoracic wall overlying a pulmonary tuberculous lesion has been attempted by many, entry being gained by resecting one or two ribs, usually in the upper interscapular region. Fat, paraffin, muscle and other substances have been introduced into the resulting extrapleural space to keep the diseased part of the lung collapsed, but these have the disadvantage of sloughing through the chest wall or into the lung in some cases. In recent years air has been used to preserve the space as in the case of intrapleural pneumothorax; the newer procedure therefore goes by the name *extrapleural pneumothorax*. The chief use of this treatment is to attempt to bring under control unstable lesions which cannot be so influenced in other ways; the prospect is that many or perhaps all of these patients eventually will need a thoracoplastic operation. Pyogenic or tuberculous infections sometimes occur in the extrapleural space and there may be a chronic serous, hemorrhagic or purulent effusion. Observation of these cases has not yet been sufficient to permit a final appraisal of the procedure.

Thoracoplasty is carried out by an extra pleural resection of the ribs over the affected part of the lung so as to release the attachments and tensions which may be preventing the closure of cavities and to exert positive compression to accelerate this process. There are various modifications of the operation designed by the surgeon according to the distribution and character of the pulmonary lesions. The most suitable type of case is that of the young patient in good general condition with no complications but with a chronic fibroid tuberculosis of one lung in which there is a small or moderate sized cavity unresponsive to rest and

them artificially if necessary There is of course nothing to do about sudden exsanguinating hemorrhages Very occasionally when the hemorrhage is large and the throat becomes filled with clots threatening death by suffocation it is possible manually to remove the clots and to revive the patient by artificial respiration or inhalation of oxygen The hemoptysis may amount to only a few small flecks or clots of blood or may vary in quantity from a few c c upward It is only occasionally that a single hemoptysis amounts to more than 100 or 200 c c

The patient with hemoptysis is placed quietly in bed preferably in a semirecumbent position so that he may expectorate easily He is reassured that the hemorrhage will stop and those about him should avoid becoming nervous or excited The patient is cautioned to spare his energy and not to cough more than necessary If he is exceedingly nervous and tense he may be given codein sulphate 30 mgm or morphine sulphate 8 to 10 mgm hypodermatically During the active bleeding this is to minimize the deep inhalations which lead to aspiration of blood containing tubercle bacilli into healthy parts of the lungs Deep sedation is inadvisable since later it may favor the retention of clots in the bronchi the ideal is to keep a balance between these opposing states

Innumerable medications have been used with the hope of controlling bleeding including coagulants such as thromboplastin intramuscularly calcium by mouth or intravenously hypertonic sodium chloride solution intravenously vasoconstrictors such as pituitrin and peripheral vasodilators such as amyl nitrite However coagulability of the blood seldom is delayed in these cases and it is doubtful whether it can be speeded Likewise I have never been convinced that the vasoconstrictors or dilators have any effect In patients having continued oozing or moderate hemoptysis sometimes I have used with possible success intravenous injections of 10 c c of 10 per cent aqueous sodium chloride solution given slowly also calcium gluconate intravenously 10 c c of 10 per cent solution In alarming cases binding of the upper part of the thighs to withhold part of the venous blood in the legs occasionally has seemed to help One cannot place much reliance on these measures however and if rest and sedation do not prove effective collapse of the lung by pneumothorax may be required

Pneumothorax for the control of bleeding involves recognition of several principles The site of the bleeding must be determined The patient may recognize it by the sensation of congestion or bubbling on one side Previous examinations may have shown the cavity and during bleeding a reliable sign is the eliciting of moist or bubbling râles on one side Unless urgent it is best not to collapse the lung during the active

absence or smallness of pulmonary cavities bronchial or laryngeal lesions should be suspected the latter especially if there is hoarseness

Coughing which is difficult to control often may be alleviated according to the cause and nature Dry irritative coughs are helped by steam inhalations which may be medicated with menthol tincture of benzoin or gomenol A useful sedative inhalation, which is dropped on gauze and held over the mouth and nose and the vapors inspired is made up as follows

Menthol	15 c c
Spirits of chloroform	30 c c
Oil of eucalyptus	60 c c

If the sputum is tenacious and difficult to raise medicines which help to stimulate the bronchial flow and liquefy the discharge may be tried these include ammonium chloride and the like Since most of these if used over long periods upset the stomach it is advisable to avoid them if possible Emetic cough occasionally occurs in advanced cases It has been found empirically that dilute hydrochloric acid the average dose being 30 c.c. in water with meals sometimes is helpful Such patients may take a drink of warm water or fruit juice before breakfast and this sometimes starts the flow of discharges which may be expelled before eating Sedatives may be used and usually it is indicated to reduce the quantity of the meals and give small feedings every three to four hours

Postural drainage should be tried in cases in which there are large cavities or in which bronchial lesions may interfere with drainage Recently Brock has been advocating keeping the foot of the bed elevated not only to permit drainage and control the cough but also for its other effects in favoring healing of the pulmonary lesions

Collapse therapy if it is effective in obliterating cavities usually eliminates the bronchial discharge and thereby the cough even before cavities are completely closed these symptoms may abate

Hemoptysis — With few exceptions hemorrhage arises in tuberculous parenchymal cavities by the erosion or rupture of blood vessels In fibroid cases without active ulceration bleeding usually in small amount may arise from dilated or distorted bronchial walls so called post tuberculous bronchiectasis less commonly from ulcers or granulations in the trachea or bronchi Bleeding from a tuberculous larynx is very rare and I have never seen it The greatest danger is posthemorrhagic pneumonia which may be partly non-specific but often continues as progressive tuberculous pneumonia chiefly in the lower lobes The principles of treatment require recognition of the facts that most hemoptyses stop spontaneously and that collapse of the lung is the surest way of controlling

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bleeding, since this interferes with the expulsive mechanisms, favors retention of blood, pneumonic complications and acute serous pleurisy. If permissible, therefore, time is allowed for the accumulated blood to be cleared out and for acute pneumonic reactions to subside before instituting pneumothorax. In extreme emergencies extrapleural pneumothorax or thoracoplasty may be performed to control bleeding.

The general management during the active bleeding includes keeping the patient warm and comfortable. The mouth may be kept moist by sips of water or chips of ice, but the old practice of feeding quantities of cracked ice is to be condemned. Likewise there is no good reason to restrict the diet to cold fluids. The patient may be given at first small quantities of warm fluid, and, as soon as he desires it, a warm soft or light diet is allowed. At first he may be nauseated and may vomit because of the swallowed blood. The bowels should be kept open, and, if necessary, a saline cathartic or an enema may be given within twenty-four to forty-eight hours. To combat the mild shock and anemia which sometimes supervene, warmth, quiet and sometimes transfusions of whole blood are helpful.

There is no doubt that the incidence of hemorrhage in this country is less than it was in former years due to earlier diagnosis, prompter treatment and a wider use of collapse therapy.

Dyspnea.—This symptom is traced to its cause and, if due to the embarrassment of a pleural effusion or pneumothorax, is treated accordingly. In other situations, such as dyspnea following hemorrhage or incident to an acute bronchitis in a case of old advanced fibroid tuberculosis, oxygen inhalation by nasal catheter may give relief until the causative condition has righted itself. I see no reason to attempt to prolong the life of a moribund patient by oxygen inhalation.

Pain.—With few exceptions pain is due to pleural involvement and is treated by placing the patient in a position which he finds most comfortable, by strapping the chest with adhesive plaster or a binder and by the use of sedatives if necessary.

Fever and Sweating.—It is seldom advisable to use antipyretics, and dependence should be placed on measures to control the fundamental pulmonary processes. Cool baths and alcohol rubs often are grateful to the patient, particularly if there is much sweating. The use of medication, such as atropin or agaricin, usually is inadequate to control sweating. Good ventilation in the room and an airy mattress are desirable, and these people feel better in a mild, cool and dry atmosphere.

Digestive Symptoms.—Anorexia and other gastric symptoms usually abate as the pulmonary process is brought under control. Mild di-

turbances should be treated mainly by adjustment of the diet according to individual caprices and indications Rigid restriction of the diet for a short time does no harm and usually proves helpful ultimately since proper digestive function is so important For the treatment of constipation it is best to avoid drugs this is controlled as a rule by proper dietary measures and the establishment of regular habits The persistence of vague indigestion particularly when this is associated with mild or moderate abdominal cramps constipation or followed by a short period of diarrhea always should lead to the suspicion of tuberculous enteritis a common complication after pulmonary cavity has developed

Anemia — The secondary anemia of tuberculosis is corrected fundamentally by control of the disease and by adequate and proper diet The addition of a suitable preparation of iron such as ferrous sulphate may be helpful Transfusions of blood have no direct effect on the tuberculosis but may be useful after severe febrile periods or serious hemoptyses

Judging the Results of Treatment

The first desideratum in the treatment of active tuberculosis is an arrest and reversal of progressive processes Such stabilization and beginning healing often is attended by complete symptomatic relief and this may be deceptive since clinical improvement is not necessarily a measure of the degree of healing of the lesions The disparity accounts for many relapses when patients perhaps with the permission of their physician resume active life prematurely In some advanced cases the best that can be hoped is quiescence of the disease which then runs a chronic slowly progressive course during the subsequent years But the earlier the diagnosis and the more limited the lesions the greater is the prospect of permanent arrest and the more important is it to apply strict criteria of satisfactory response Disappearance of symptoms is only one guide Satisfaction of the criteria requires that anatomical healing be durably established Physical examination alone does not determine this and the two most important tests are the sputum examination and serial x ray examination The roentgenograph should show stationary shadows of a diffuse linear or nodular character indicating well developed fibrosis and no cavities should be recognizable Since small cavities and ulcers may escape detection in the roentgenograph it is most important to establish that the other evidence of ulceration viz tubercle bacilli in the sputum is not present The sputum if any may be scanty and should be collected for a few days or perhaps as long as two weeks

for concentration culture and animal inoculation When by these tests the pulmonary lesions have remained fibrotic and stationary, and tubercle bacilli have not been demonstrable for a period of six months the classification of the National Tuberculosis Association permits calling the case an arrested one However experiences show the desirability of preserving these conditions for at least two years in order to obtain the best guarantee of a permanent arrest It is assumed of course that any tuberculous lesions elsewhere in the body likewise are well healed

Tuberculous Complications

Tuberculous laryngitis and *tuberculous enteritis* are the two most common complications of cavernous pulmonary disease rarely occurring before the cavity has formed Alertness for these possible developments therefore is necessary The larynx should be examined at intervals particularly if there is the slightest suggestion of tickling dryness or hoarseness Enteritis is suspected if typical colic and diarrhea occur but should be diagnosed before this if possible Vague symptoms such as fatigue failure to gain weight and anemia out of proportion to the pulmonary lesions should awaken suspicion and lead to proper x ray examination There is always a basis for symptoms and any odd behavior of the case should lead invariably to a search for the cause Otherwise insidiously developing complications often escape notice and get beyond control before they are identified While the patient must not become too introspective it is a mistake to belittle or ignore slight symptoms the treatment of which may spell the difference between recovery and relapse See following pages for various tuberculous complications

Non tuberculous Complications

Tuberculous patients are subject to all the other ills of the flesh and these may have a decided bearing on the prognosis

Amyloid disease is seen most commonly in the presence of chronic tuberculous abscesses such as empyema and with bone and joint tuberculosis Pulmonary cases do not develop it as a rule to a great degree unless there is a complicating tuberculous enteritis Its progress is best arrested by control of the pulmonary disease amyloid deposits have been reported to be absorbed in some cases The administration of liver extract is believed to be helpful but the experience is not conclusive

Diabetes mellitus when uncontrolled is generally known to favor the

development and progression of pulmonary tuberculosis which has a striking tendency to caseate rapidly in this combination It is important to institute treatment for the diabetes promptly by means of the accepted dietary measures with the use of plain or protamine insulin if necessary If possible this should be done before instituting collapse therapy since the possible development of a febrile pleural effusion may render both conditions difficult to control

Syphilis if it is active seems to lower resistance against tuberculosis and impair the prognosis Often there is a fear that antisyphilitic therapy may produce unfavorable reactions in the tuberculous lesion but this effect varies widely In the case of chronic fibroid tuberculosis the customary course of arsenical drugs usually is well tolerated However in the case of early tuberculosis of an exudative pneumonic character the administration of the metallic drugs may stimulate an unfavorable focal reaction with fever and progression of the tuberculosis In these cases therefore a slowly absorbed drug such as a preparation of bismuth or of bismuth and arsenic may be administered intramuscularly When the balance is not so delicate neoarsphenamine may be given in the usual way starting with one half to one third the standard dose and increasing slowly the size of the subsequent doses In the case of primary or infectious syphilis vigorous antisyphilitic therapy usually should be given regardless of the tuberculosis if the latter is judged to be the minor hazard In the case of chronic fibrocavernous tuberculosis in an old patient with inactive syphilis it may be inadvisable and futile to attempt to treat the latter Iodides are not given in tuberculous cases but the other drugs usually are not harmful if used with judgment and caution

Hyperthyroidism if active may lead to impairment of resistance against tuberculosis Thyroidectomy preceded by a short course of iodine therapy usually is well tolerated and eventually may improve the general prognosis

Pregnancy varies in its effect on tuberculous women As a rule it should be avoided until the pulmonary disease has been arrested for at least two years During the early months the vomiting and other disturbances of pregnancy may undermine resistance and in some cases the puerperium is not well tolerated Many women however do well in the last two trimesters Some are broken down afterwards by the work anxiety and loss of rest incident to the care of the child Some women with tuberculosis well controlled by penumothorax or even by thoracoplasty have tolerated pregnancy well In the case of recently developed exudative tuberculosis in any active case and in advanced fibroid cases even though arrested therapeutic abortion usually is advisable if the preg

nancy is recognized during the first trimester Otherwise usually it is decided to allow the pregnancy to proceed the method of delivery being decided at term Some favor Caesarian section but others do not because it is a major operation with a mortality rate varying up to 4 per cent A woman with open infectious cavitary tuberculosis should not nurse her child Every woman who contemplates pregnancy should have a physical examination and this should include a roentgenograph of the chest to rule out tuberculosis

Heart disease when present is treated the same as in non tuberculous patients In the case of mitral stenosis the tuberculosis often runs a mild and protracted course being favorably influenced apparently by the pulmonary congestion Old tuberculous patients with arteriosclerosis usually do badly In advanced bilateral fibroid tuberculosis even though this is arrested the obstruction of the pulmonary circulation may throw an increasing strain on the right heart leading to hypertrophy of the right ventricle which eventually may dilate and fail with the development of visceral congestion and anasarca Such patients must limit their activities very strictly

Acute respiratory infections such as a common cold and pneumonia are treated in the usual way but the patient is cautioned always to go to bed promptly and to remain there until convalescence is completed Patients with arrested tuberculosis if not too extensive tolerate these acute infections very well Otherwise especially in cavernous cases aggravation may occur sometimes with hemoptysis Suppurative pneumonia leading to lung abscess often aggravates existing tuberculosis in the same lung The acute pyogenic necrosis may break down well healed tubercles and lead to a relapse

Silicosis not only favors the development of tuberculosis but also as a rule renders its treatment most difficult These patients do not tolerate collapse therapy well and once the tuberculosis becomes progressive usually it is intractable

Asthma is treated in the usual way except that iodides are avoided Protein desensitization in these cases should be carried out cautiously avoiding any constitutional reactions since non specific protein therapy at times has led to aggravation of the tuberculous lesions In arrested cases desensitization is not contraindicated if this precaution is observed In active and progressive cases of tuberculosis it is better if possible to avoid the irritant by a change of environment

Anesthesia and surgical operations frequently are necessary in tuberculous patients and may be well tolerated It is always desirable to avoid ether anesthesia since this is irritating and may cause copious bronchor

rhea leading to bronchogenic dissemination of the infection Local anesthesia or the use of gas inhalation is preferable Some prefer of the gases cyclopropane but the danger of explosion in its use must be remembered and special precautions against it taken

Aftercare and Rehabilitation

The patient should be advised of the necessity of most careful living and supervision for at least two years after the pulmonary disease has become arrested His family should be advised about the nature of the disease and the desirability of cooperation Otherwise the patient often is shamed or cajoled into exceeding his limitations and this has been responsible for many relapses Kind friends often do the same and patients should be warned to give no heed to lay advice Home conditions should permit the patient's having seclusion for his rest in the afternoon and for his night's sleep His activities must be guided by the physician as they were during the period of treatment so that a sufficient interval is allowed after an increase to test his tolerance Recurrence of symptoms if any must be noted but it is important to recognize that unfavorable changes in the lesions usually precede clinical manifestations The weight is recorded periodically during the resumption of physical activities excess adipose tissue often is lost without harm Periodical x ray and sputum examination should be carried out at first every month later increasing the interval to two or three months after the first two years to six months Every ex patient should have an examination at least once a year indefinitely and oftener if there is the slightest suggestion of recurrent symptoms As part of this examination the erythrocyte sedimentation rate may be estimated but this is less important than a careful and skillful study and interpretation of the roentgenograph and the sputum test

Patients who have not followed laborious occupations do best as a rule to return to former working conditions Others often have to be reeducated in some new trade or profession and for this purpose institutions like the Altro Work Shops and the Potts Memorial Hospital in the United States are ideal Such retraining is carried out on a graduated scale over a period of months or several years

The problem of the chronic cavernous case which is not suitable for artificial collapse therapy is ever present These people may live for many years if they are able to limit their activities markedly They often become public charges and if they are irresponsible they constitute a grave menace because they are sources of infection in the community

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some nearby or distant focus or by invasion from adjacent structures such as a rib or vertebra. Occasionally in hematogenous tuberculosis the parietal pleura alone is sprinkled with miliary tubercles.

Localized Pleurisy.—Localized forms are most common and the lesions usually overlie those in the lung, the upper and posterior parts of the pleural membrane being the favored points. The pleura presumably may be involved without direct bacterial invasion in the perifocal inflammation about a tuberculous focus at some distance beneath the surface of the lung, and as this subsides organizing adhesions may be left behind. There is reason to believe, however, that actual invasion by the tubercle bacillus usually is responsible. The reaction is represented either by tubercle formation or more often by diffuse edema and cellular and fibrinous infiltration in the pleura and on its surface. The latter becomes dull and rough and superficial fibrin deposits soon may appear. Extension to the adjacent parietal pleura is the rule, and a similar but usually less intense change occurs here. The surfaces become agglutinated, and the later organization of the exudate leads to permanent fibrous adhesions. Fibrinous adhesions may be absorbed, leaving a barely discernible patch of thickening. Early fibrinous agglutination of the surfaces apparently is the mechanism which confines the pleurisy and prevents infection of the entire membrane. The great frequency of diffuse sero-fibrinous inflammations in the pleura following artificial pneumothorax apparently is explained by the mechanical separation of the visceral and parietal layers preventing such agglutination and localization.

The successive and isolated invasions of the pleura in chronic pulmonary disease lead to the formation of multiple isolated adhesions varying from minute strings to extensive areas in which the layers are completely inseparable. Eventually the adhesions may have a structure varying from loose areolar tissue to firm, almost cartilaginous sheets. This is of clinical importance since it determines to what extent adhesion may interfere with the successful application of artificial pneumothorax, whether they will stretch in the course of this treatment or whether they may be sectioned surgically. Adhesions usually are somewhat vascular and sometimes bear well developed vessels; circulation in the tuberculous lung then may be partly maintained by a supply of blood coming through the adhesions from the chest wall. Likewise such adhesions may bear lymphatics, and this explains certain odd findings such as the presence of anthracotic lymph nodes in the axilla. Diffuse involvement of the pleura may be due to successive localized fibrinous inflammations or to a generalized inflammation, usually of a serofibrinous type.

Serofibrinous Pleurisy.—The distinction between fibrinous and sero-

It is often necessary therefore to provide permanent shelter and care for them in order to safeguard others

Relationships between Pulmonary and Extrapulmonary Tuberculous Lesions

It is helpful in diagnosis and prognosis to understand the relationships of pulmonary and extra pulmonary lesions the conditions under which the development of the latter may be anticipated and the means of early diagnosis and prevention Descriptions of some of these extra pulmonary lesions are given in other chapters of Oxford Medicine but because of the relationships some of the clinical features are discussed here

Dissemination of tubercle bacilli from lesions in the lung may occur by erosion of a pulmonary vein accounting for certain cases of terminal generalized miliary disease but this is more common when the lymph nodes of the mediastinum are involved particularly in childhood On the other hand it is most unusual to see tuberculous involvement of the alimentary tract larynx or pharynx except as a complication of cavernous pulmonary tuberculosis in adults The constancy of this relationship and its rarity in cases of strictly lympho hematogenous tuberculosis suggests that the usual mechanism of infection is by surface contamination with the discharges arising from pulmonary cavities The tracheobronchial and alimentary canals are very resistant to infection when one considers their frequent contact with tubercle bacilli and it is only occasionally that they are diseased The structure of the tissue and previous traumatization apparently have some influence and a seemingly important factor is the duration of the contact with the infectious material Thus the accumulation of discharges in the larynx during sleep and the slowness of the passage of intestinal contents through the cecum may account for prolonged contact and the frequency of lesions at these sites Appreciation of these possibilities is of great importance in diagnosis since the finding of healthy lungs weighs strongly against tuberculosis in the mouth pharynx larynx or gastrointestinal tract when the nature of these lesions is in question On the contrary in any case of cavernous pulmonary tuberculosis the possibility of development of lesions at these other sites is always to be considered

Tuberculosis of the Pleura

Infection of the pleura occurs most often by direct or lymphatic extension from the lung but also by hematogenous dissemination from

and caseous matter may be retained and these may be the sites of calcareous changes in later years Usually such calcification is not recognized until five to ten years afterward

Hemorrhagic Pleurisy — Hemorrhagic pleurisy may result from several mechanisms in tuberculosis In serofibrinous inflammation the reaction may be so intense that the membrane has a fiery red appearance and the exudate may take on a sanguinolent tinge due to the extravasation of red blood cells In rare case acute effusions consisting of pure or almost pure blood hemothorax are caused by the rupture of the pleura establishing a communication with a tuberculous cavity in which a blood vessel also has been torn Another cause of bloody effusions likewise very uncommon is the rupture of an adherent emphysematous part of the lung these changes being due to a more or less healed tuberculous lesion Here as in the former instance pneumothorax is produced and a large amount of blood may accumulate rapidly in the pleural space In either event subsequent changes depend first on the irritating properties of the blood and secondly on infection Blood alone is irritating causes an outpouring of serum and results at first in fibrinous and later in fibrous and occasionally calcareous changes As described further along rupture of the pleura may lead to tuberculous or mixed infection and the changes subsequent to hemorrhagic effusion will depend largely on this

Ulceration or Rupture of the Pleura with Bronchopleural Fistula and Spontaneous Pneumothorax — Small caseous tubercles may ulcerate through the pleura without causing a bronchopleural fistula because if the process is slow agglutination of the pleural surfaces will localize and seal off the involved area This phenomenon doubtless explains such observations as the following

When bronchopleural fistula occurs the perforation as Powell and Hartley showed is (1) usually in the upper half of the lung though rarely higher than the third rib since above this point the pleural cavity generally is obliterated by adhesions (2) ulceration of the pleura appears to be more common in acute caseous pulmonary tuberculosis than in the chronic fibrous form due to the fact that the adhesive process has not had time to develop in the former (3) ulceration of the pleura is more common after artificial pneumothorax since there is no possibility of this protective mechanism operating once the pleural layers are separated

The common mechanisms of pleural perforation are (1) ulceration of a subpleural or pleural caseous focus (2) rupture of a pleural bleb associated with the tuberculous lesion (3) tearing of the pleura by the trac

fibrinous pleurisy is only one of degree and intensity The rule has been worked out experimentally by Patterson and others that acute serous exudations can be produced promptly after infection only in allergic animals The reaction is intensified and accelerated on account of the hypersensitivity of the tissues and also in some cases by the size of the infecting dose of tubercle bacilli Thus the ulceration of a caseous tubercle into the pleura permitting the discharge of a large mass of infection almost inevitably leads to acute serofibrinous inflammation Similarly multiple invasions in the course of acute hematogenous dissemination undoubtedly accounts for the rather common observation of serous effusions in one or both pleural cavities In these situations the pleura shows varying degrees of edema redness lack of luster and roughness The exudate which usually is serous but sometimes serosanguineous may be slight or it may fill the pleural cavity with displacement of the containing walls Rather rarely the lesions may be progressive and the pleura may become caseous generally however the acute inflammatory phase is followed by the stages of absorption and healing The pleural surface becomes coated with fibrin and the free exudate lessens acquires a content of coagulated fibrin flakes or strands and eventually disappears The fibrinous and granulating visceral and parietal surfaces become agglutinated and eventually the lung becomes rather completely bound to the parietal pleura by firm fibrous adhesions See also Pleurisy with Effusion in Chapt X Vol II

Tuberculous Empyema — Tuberculous empyema generally is to be interpreted as an aggravated phase of serofibrinous pleurisy It is observed most frequently when the pleura has become infected following the ulceration and rupture of a caseous pulmonary focus It is also a complication of artificial pneumothorax treatment in from 5 to 10 per cent of the cases depending on the character of the underlying lesion and the duration of treatment In the former case because of the acuteness and intensity of the infection tuberculous empyema often develops rapidly The initial intense inflammation is followed soon by the deposit of a shaggy fibrinous membrane which may attain a thickness of several centimeters In severe cases the fibrin layers may undergo caseous and colliquative necrosis While the empyema may be serious in itself it often has a great tendency to heal in which case it leaves behind deep dense and extensive fibrosis This massive organization leads to mechanical retractions which are much more conspicuous than after simple fibrinous or serous pleurisy The chest wall diaphragm heart and mediastinum may be greatly retracted and more or less ankylosed Within the organizing layers the residues of somewhat inspissated tuberculous pu

and caseous matter may be retained and these may be the sites of calcareous changes in later years Usually such calcification is not recognized until five to ten years afterward

Hemorrhagic Pleurisy — Hemorrhagic pleurisy may result from several mechanisms in tuberculosis In serofibrinous inflammation the reaction may be so intense that the membrane has a fiery red appearance and the exudate may take on a sanguinolent tinge due to the extravasation of red blood cells In rare case acute effusions consisting of pure or almost pure blood hemothorax are caused by the rupture of the pleura establishing a communication with a tuberculous cavity in which a blood vessel also has been torn Another cause of bloody effusions likewise very uncommon is the rupture of an adherent emphysematous part of the lung these changes being due to a more or less healed tuberculous lesion Here as in the former instance pneumothorax is produced and a large amount of blood may accumulate rapidly in the pleural space In either event subsequent changes depend first on the irritating properties of the blood and secondly on infection Blood alone is irritating causes an outpouring of serum and results at first in fibrinous and later in fibrous and occasionally calcareous changes As described further along rupture of the pleura may lead to tuberculous or mixed infection and the changes subsequent to hemorrhagic effusion will depend largely on this

Ulceration or Rupture of the Pleura with Bronchopleural Fistula and Spontaneous Pneumothorax — Small caseous tubercles may ulcerate through the pleura without causing a bronchopleural fistula because if the process is slow agglutination of the pleural surfaces will localize and seal off the involved area This phenomenon doubtless explains such observations as the following

When bronchopleural fistula occurs the perforation as Powell and Hartley showed is (1) usually in the upper half of the lung though rarely higher than the third rib since above this point the pleural cavity generally is obliterated by adhesions (2) ulceration of the pleura appears to be more common in acute caseous pulmonary tuberculosis than in the chronic fibrous form due to the fact that the adhesive process has not had time to develop in the former (3) ulceration of the pleura is more common after artificial pneumothorax since there is no possibility of this protective mechanism operating once the pleural layers are separated

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tion of an adhesion Of these the last seems to be the least frequent a the point of their insertion on the lung fibrous adhesions u ually are at tached to a thickened visceral layer which is not easily ruptured It is possible however that mechanical traction from an adhesion might at times favor the rupture of an adjacent area of the pleura already thinned out by an underlying caseous necrotic process The other two mechan isms are mainly to be considered If the pleura has become thinned and weakened by the atrophic changes which accompany fibrosis and emphy sema rupture may occur through the weakened point The consequence then may be quite similar to non tuberculous spontaneous pneumothorax If no tubercle bacilli escape through the pleural perforation the pneumo thorax remains sterile likewise the pleural fistula itself is not infected and following collapse of the lung usually heals rapidly Little or no effusion occurs in the pneumothorax and following reexpansion the pre vious condition of the lung and pleura may be restored

Conditions are different however when a liquefied caseous lesion sloughs through the visceral pleura first because of the widely liberated infection and secondly because the point of perforation represents an infected and inflammatory process in itself In addition to the collapse of the lung the event practically invariably is followed by an acute tuber culous pleurisy with effusion This may follow the course of the pro tracted inflammation described above or secondary pyogenic infection may be superadded to convert it into a mixed infection empyema The tuberculous fistula in the visceral pleura as a rule becomes chronic and seldom heals except under special treatment Tubercle bacilli and pyo genic organisms are discharged constantly from it and should the fi tula communicate with a pulmonary cavity the contents of the latter may drain continually into the pleural space The reverse also may occur viz drainage of the pleural exudate through the fistula into the lung to cause further infection there

Fibrinous Pleurisy — Symptoms If the subpleural lesions are small and only mildly active the patient may have had no premonitory warn ing otherwise there may have been suggestive or manifest symptoms of pulmonary tuberculosis The pleurisy may start with severe stabbing pain in the chest with soreness and an occasional stitch in the side or with no pain whatsoever Since the inflammation usually is self limited symptoms usually are of short duration In the presence of more intense and extensive involvement each inspiratory effort may be distressingly painful and the patient may be obliged to lie with the affected side splinted The site of the pain varies It may be directly over the point of involvement or by reference along the course of the spinal cutaneous

segments or the cutaneous distribution of the phrenic nerve in case the diaphragmatic pleura is involved Thus it may be felt over a wide section of the chest wall along the trapezius ridge or in the upper abdominal wall While breathing may be short and restrained there is no cyanosis Sometimes the pleural irritation may cause a short dry cough

The temperature shows little or no elevation One to two degrees of fever may be noticed in the afternoon or evening but usually only for several days at most Chilliness is not a feature nor night sweats unless there are other causes The patient may recall having had previous attacks The duration of acutely painful symptoms ordinarily is short lasting three or four days but occasionally a constant or intermittent usually dull and sore pain persists for many weeks During this time the temperature may be slightly elevated occasionally the pulse may be unstable and slightly accelerated and the patient may have undue fatigue and a loss of a few pound in weight Symptoms of tuberculous involvement elsewhere are not uncommon The patient s distress may be objectively evident by the short breathing and the instinctive splinting of the affected hemithorax Hyperesthesia of the skin sometimes may be detected by lightly stroking or pinching along the spinal cutaneous segments Auscultation may reveal a friction rub over a small or wide area sometimes only a few superficial pleural crepitations and sometimes none at all particularly if other than the parietal surfaces are involved Coarse rubs may be palpable It is an interesting observation that the rub may be most evident a few days or a couple of weeks after the acute pain has subsided due presumably to the fact that the fibrinous coating has protected the pleura against painful stimuli The roentgenograph as a rule shows nothing except the signs of any preexisting pulmonary lesions although fluoroscopy like the physical examination may reveal limitation of the movement of the thoracic wall and diaphragm

Diagnosis of Fibrinous Pleurisy — The most important diagnostic point is the determination of associated pulmonary lesions of tuberculosis which if proved is evidence enough In cases in which the lungs apparently are clear the possibility of tuberculous pleurisy is not ruled out since the pulmonary lesions may be so small or so peculiarly situated as to escape detection In addition to the symptoms and signs described the most important point is the elimination of other possible causes such as non tuberculous inflammations in the lung generalized infections malignant invasion and cardiorenal lesions The age of the patient is of some importance since barring an acute respiratory infection the most common cause of pleurisy in a young person is tuberculosis The *treatment* during the active phases is rest in bed The pain may be relieved

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homogeneous shadow over the base of one lung rising from the median line to a higher level in the axillary line the upper limits being soft and hazy The diagnosis is substantiated by thoracentesis which yields fluid usually of a clear and straw colored character This has the characteristics of an inflammatory exudate and if considerable quantities of it are treated by high speed centrifugation tubercle bacilli often can be demonstrated by culture or guinea pig inoculation less often by direct microscopic examination

The *differential diagnosis* of serofibrinous pleurisy includes consideration of other acute infections such as serous inflammations of the pleura associated with pneumonia malignant disease cardiorenal disease and Hodgkins disease The differentiation usually is not difficult Pneumonia may be diagnosed wrongly because the basal dullness skodaic resonance and distant bronchial breath sounds of a pleural effusion occasionally simulate the signs of a consolidated lobe particularly if the pleura is partially adherent In such instances the lack of a history of acute catarrhal inflammation of the respiratory tract is most important Thoracentesis may settle the question unless there is a serous effusion associated with pneumonia

Pneumonic effusions usually become absorbed within a week or two following the onset or become purulent whereas tuberculous effusions usually persist longer remaining serous or serofibrinous all the while In the absence of cardiorenal disease or an acute catarrhal respiratory infection the development of pleurisy with effusion in a young person is almost invariably a sign of tuberculosis and this assumption may be substantiated later by the clinical course and the finding of the bacillus Malignant disease is a consideration in older people in which case one searches for other evidence remembering that pleural effusions are more common as an early accompaniment of metastatic neoplasms than of primary bronchogenic carcinoma The effusion may be sanguinolent or sanguineous in tuberculosis or malignant conditions somewhat more often in the latter Final differentiation may be made on the basis of the clinical course the finding of tubercle bacilli or when other suspicions are aroused the finding of malignant cell in the embedded and sectioned sediment of the centrifuged pleural exudate The effusion of Hodgkins disease may resemble that of tuberculosis but the condition usually is distinguished by the finding of other lesions characteristic of one or the other disease

Clinical Course and Treatment of Serofibrinous Pleurisy — Tuberculous pleurisy with effusion occasionally may run a mild course and even may be unrecognized throughout More often after the onset fever continue

by strapping the chest After the acute symptoms have subsided or sooner a roentgenograph of the chest should be made to determine the condition of the lungs If a pulmonary lesion is found treatment of this is continued if not the patient may be allowed gradually to resume his activities If tuberculosis is strongly suspected two to six months may be desirable for convalescence During this time and afterwards the patient should be carefully examined at intervals of six months and then a year to detect possible exacerbations of the infection

Serofibrinous Pleurisy — The onset of pleurisy with effusion usually is abrupt but occasionally insidious following acute or recurrent fibrinous pleurisy of some duration If the patient previously has had pulmonary tuberculosis the symptoms may be attributed to this alone and the complication may go unrecognized at least until mechanical or other striking symptoms first suggest its presence Often however the source of the pleural infection is in some nearby or distant focus the latency of which accounts for the patient s previous well being The insidious onset following protracted fibrinous pleurisy is represented as a rule by mild or moderate toxemia with fever rising in the evenings one or two degrees sometimes more The pain of the dry pleurisy may disappear as the sensitive surfaces are separated by the serous effusion More commonly the initial symptoms are more acute and severe the patient may experience a sudden stabbing pain in the chest chilliness rapid rise of temperature flushing sweating and soon after this difficulty in breathing with a feeling of fullness in the chest Sometimes there is a slight irritative cough but this usually is lacking unless there is an underlying pulmonary lesion of some consequence Areas of hyperesthesia of the skin on the affected side may be indicated by sensitiveness to slight stimuli The diagnosis depends first on consideration of the symptomatology which should be analyzed carefully particularly as to the nature of any symptoms preceding the abrupt episode The sharp pain fever and respiratory difficulty slowly increasing should arouse suspicion especially when there have been no symptoms of acute catarrhal infection of the respiratory tract

Physical examination reveals signs which vary according to the amount of fluid present the most important being dullness and diminution of breath sounds and vocal fremitus at the base of the lung on one side and slight or moderate displacement of the heart to the opposite side Large effusions may produce marked dyspnea bulging of the intercostal spaces and marked displacement of the mediastinum and diaphragm Associated signs of parenchymal involvement may be noted by physical and x ray examination Characteristically the roentgenograph shows a diffuse

homogeneous shadow over the base of one lung rising from the median line to a higher level in the axillary line the upper limits being soft and hazy The diagnosis is substantiated by thoracentesis which yields fluid usually of a clear and straw colored character This has the characteristics of an inflammatory exudate and if considerable quantities of it are treated by high speed centrifugation tubercle bacilli often can be demonstrated by culture or guinea pig inoculation less often by direct microscopic examination

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with afternoon rises to 103° F to 105° F for two to four weeks, after which it subsides slowly by lysis by the end of the sixth or eighth week exceptionally the febrile course continues for three months or longer The associated prostration loss of weight and tachycardia are typical of tuberculosis Massive effusions cause marked dyspnea distress and cyanosis Treatment consists of rest in bed and good nursing during the febrile stages Thoracentesis is performed for several reasons first it is advisable for diagnostic purposes at least 500 c c of fluid being removed if possible second the fluid may be evacuated in quantities of 500 to 1000 c c at intervals of several days or a week to relieve the mechanical symptoms and finally during defervescence if the fluid absorbs very slowly aspiration of the residue may be indicated to favor more rapid expansion of the lung Replacement of the aspirated fluid with a small quantity of air may be desirable if an underlying parenchymal lesion is suspected and one wishes to visualize it by x ray Artificial pneumothorax sometimes should be continued if the pulmonary lesion makes it necessary Otherwise artificial pneumothorax is strictly contraindicated since it does not prevent the formation of adhesions but preserves a dead space in the pleura retards the absorption of effusion and favors chronicity and eventually fibrous organization of the pleura

The subsequent treatment of the patient is important Even though no lesions are demonstrated in the pulmonary parenchyma it must be assumed that the tuberculous pleurisy originated from some preexisting focus here or elsewhere which became active and that the pleurisy itself represents an active phase of tuberculosis These patients therefore usually need a period of sanatorium or rest cure for at least six months after the fever has subsided During this time they may resume physical activity gradually approaching normal life In the presence of underlying parenchymal lesions the treatment is modified accordingly The prognosis of pleurisy with effusion properly treated is excellent as indicated by the study of Trudeau There have been numerous experiences however to show that the liability to the later development of pulmonary tuberculosis especially if sanatorium treatment or its equivalent is omitted is great Kallner s recent report reveals that about 39 per cent of his large group of patients developed pulmonary tuberculosis after pleurisy and that at least 22 per cent died The pulmonary disease usually appears within five years

Empyema of the Pleura — Clinically the transition between serofibrinous pleurisy and tuberculous empyema is not always distinct The character of the exudate is the chief means of differentiation Mere clouding of the fluid with flakes of fibrin and intact mononuclear cells is

not sufficient to call it empyematous. The latter term is reserved to designate cases in which the fluid is thick, creamy and contains many mononuclear and pus cells, many of which are broken down, and also a large content of fibrin which may be partly degenerated. The number of tubercle bacilli in the exudate is not in itself a criterion of distinction, although it may be said that organisms usually are scarce in serous effusions and may be numerous in purulent ones. The disease is almost always secondary to a lesion in the lung or adjacent structure and is most often a later development of serofibrinous pleurisy. Intermediate transitional stages may be characterized as seropurulent pleurisy.

The *clinical course* of tuberculous empyema may be acute, subacute or chronic, and the seropurulent or purulent exudate may develop within a few weeks or several months after the onset. More commonly, however, the transition is slow, and the clinical course is subacute or chronic, extending over many months or years. Chronic empyema is found usually in the presence of pneumothorax which may be due to the rupture of subpleural tubercles or to previous artificial induction. The symptoms do not differ materially from those of serofibrinous pleurisy in so far as local manifestations are concerned. The chief difference with relation to constitutional symptoms is the failure of the process to limit itself within the customary six to eight to twelve weeks and the continuation of fever and other symptoms of toxemia for long periods of time. After the pleura has become greatly thickened, absorption from it into the circulation may be so minimized that the fever subsides, and the general condition becomes good, even though the purulent exudate continues forming. In some cases eventually the effusion gradually resumes a serous character and may be completely absorbed.

The resulting fibrosis of the pleura and underlying lung may hinder or completely prevent full reexpansion of the lung. The pleural dead space then may become filled with a transudate, and retraction of the mediastinum, chest wall and diaphragm occurs. The patient may notice gradual shrinking and flattening of one side of the chest, may experience dull, sore pains here for many years, especially during changeable weather and on becoming fatigued, and may develop considerable scoliosis (*thoracogenic scoliosis*). The physical and roentgenographic signs are those common to any exudative and organizing pleurisy. The common complications and sequels, in addition to mechanical retractions, include secondary pyogenic infection entering through a bronchopleural fistula or accidentally introduced during thoracentesis, amyloidosis which sometimes becomes very extensive and pronounced, and sinuses and abscesses of the chest wall, resulting most often from infection of needle tracks.

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Tuberculosis of Other Serous Membranes

Any of the serous membranes may become tuberculous and although the incidence has declined greatly in the United States the disease still is not uncommon The infection may remain confined to one serous cavity or affect several or all simultaneously or successively *polyserositis* multiple involvement occurs most often in the course of acute subacute or chronic hematogenous tuberculosis Infection of the *pericardium* may occur by way of the blood or lymphatic streams or by invasion from a diseased adjacent structure The resulting lesion may be subacute localized fibrinous pericarditis acute serofibrinous pericarditis or chronic fibrous and adhesive pericarditis The serofibrinous type may be difficult to distinguish from other kinds of pericardial effusion the diagnosis depends on the identification of tuberculous lesions elsewhere observation of the clinical course and the bacteriological study of the aspirated fluid Chronic adhesive pericarditis may ensue eventually and this may become so constrictive as to cause serious functional cardiocirculatory disturbances

Localized lesions of the *visceral peritoneum* are frequent in association with tuberculou enteritis Diffuse involvement usually is traceable to hematogenous dissemination of the infection or to direct extension from caseous nodes in the abdomen or tuberculous salpingitis The inflammation may be fibrinou serofibrinous or of a chronic adhesive and hyperplastic type the latter usually being a sequence of one of the acute forms

Tuberculosis of the Bronchi and Trachea

In most cases of pulmonary tuberculosis there is some involvement of the smaller bronchi in the vicinity of the parenchymal lesions This i not distinguished clinically and no particular treatment is indicated However when occasionally lesions develop in the larger bronchi and trachea these in themselves may have an important bearing on the behavior and treatment of the case The incidence has been variously estimated and at autopsy has been found grossly in 3 1 per cent of 285 cases by Flance and Wheeler The bronchi most often affected are those which drain a tuberculous cavity However there are lesions which develop as the result of invasion of the wall of the trachea or bronchus from a tuberculous node in the mediastinum usually at or near the lower end of the trachea or the main bronchi In the latter event perforation of the caseous lesion into a bronchus may be responsible for infection of

Empyema necessitatis may develop but rupture through the visceral pleura into the lung is more common than through the thoracic wall

The *treatment* of tuberculous empyema consists in local measures in addition to those which usually are under way for the pulmonary condition In the acute uncomplicated cases the fluid may have to be aspirated from time to time to relieve mechanical symptoms At times this also alleviates the toxemia but in other cases there is a febrile reaction following every thoracentesis Since final healing is conditioned upon complete obliteration of the space it is unwise to introduce air into the pleural cavity and if artificial pneumothorax already is in use it may be necessary to discontinue this in an attempt to reexpand the lung before fibrous changes make it impossible Otherwise unless by good fortune the empyema heals itself thoracoplasty eventually may be necessary to obliterate the pleural space by bringing the parietal and visceral membranes into contact

If the serous or purulent effusion is complicated by secondary infection provided no bronchopleural fistula is present antiseptic irrigations may be used through a closed system The methods employed for this in the Tuberculosis Service in Bellevue Hospital have been described by Riggins and Amberson For Gram positive aerobic cocci solutions of gentian or crystal violet prove effective chlorine solutions, such as azochloramide are useful for certain other organisms the anaerobic infections are most difficult to treat and thoracotomy for drainage may be necessary Unless it is obligatory however tuberculous empyema without a bronchopleural fistula should not be drained surgically because of the danger of a tuberculous fistula which usually persists at the site in the chest wall In a great majority of cases of tuberculous empyema associated with a bronchopleural fistula secondary infection from the respiratory tract occurs The exudate frequently accumulates rapidly and if this leaks through the pleural fistula into the bronchi aspirational tuberculous pneumonia of the lungs often results This most serious situation may be complicated further by the gaseous tensions in the pleura created by the valve mechanism of the fistula The pleural fistula seldom heals unless the visceral and parietal layers can be approximated consequently early thoracotomy usually is indicated for drainage and later thoracoplasty to obliterate the pleural space The complication is dangerous and less than half the patients who develop bronchopleural fistulas with tuberculous empyema eventually recover

Sacculated Effusions — Sacculated serous or purulent effusions may be confined to any part of the main pleural cavity or of the interlobar fissures Diagnosis is best accomplished by special oblique and lateral roentgenographic views

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the pulmonary parenchyma which previously was clear Most of the lesions are small and superficial appearing as localized infiltrations which may slough leaving behind shallow lenticular ulcers surrounded by diffuse reddening and edema of the mucosa These usually are single but may be numerous In other cases the invasion of the tracheal or bronchial wall is deeper leading to marked infiltration more or less fibrosis and sometimes deep ulcers and granulations which may heap up in the form of a localized tumor tuberculous granuloma After healing the bronchial mucosa may be restored or there may be local scars which if extensive lead to stenosis of the canal

Obstructing granulations or stenoses may interfere with normal drainage of the bronchi beyond the point of involvement and this in turn may favor the development of acute or chronic suppurative pneumonic lesions As a consequence the affected part of the lung may become involved in a mixed process Occasionally this mechanism leading to necrosis of the parenchyma is responsible for the breaking down and activation of tuberculous lesions which previously were healed The sudden increase in the size of thin walled cavities in some cases may be due to partial obstruction of the efferent bronchus which causes an inflation of the cavity by its interference with normal ventilation check valve mechanism Similarly obstructive emphysema of one lung may occur In still other cases the persistence of tracheobronchial lesions after the pulmonary lesions have become arrested creates troublesome situations such as a continuing discharge of pus bearing tubercle bacilli which may lead to other complications or a gradually increasing stenosis which may cause dyspnea and other symptoms The symptoms vary according to the extent and location of the lesion

In a patient with pulmonary tuberculosis the condition may be suggested by the complaint of wheezing respiration particularly if this is localized to one side of the chest and is aggravated by acute catarrhal infections The cough may be more pronounced than would be anticipated from the pulmonary lesions alone and likewise the quantity of the sputum may be greater and of a more mucoid character If secondary suppuration has occurred the sputum may be profuse purulent and even foul In the presence of extensive bronchial lesions the patient has almost continuous wheezing respiration may be dyspneic and even somewhat cyanotic Stridulous breathing is rare Hemoptyses from such lesions may occur while copious bleeding has been observed from deep ulcerations this is rare also As a rule there is only streaking of the sputum and then the probability is that the bleeding arises in the lung rather than in the bronchus In cases in which there is no parenchymal

disease but in which there is a bronchial lesion due to ulceration from an adjacent lymph node the patient may cough wheeze and expectorate mucopurulent sputum Constitutional symptoms depend as a rule on the activity of the associated lesions and not on the tracheobronchial lesions alone

Physical examination as a rule is more helpful than the x ray The most suggestive finding is a wheezing rhonchus heard in the middle of the interscapular area or in the parasternal region particularly near the second or third intercostal space The rhonchal sounds may be widely propagated throughout a lobe or the entire lung and may be audible at the patient s open mouth When the trachea is involved extensively the wheezing rhonchi may be heard along its course and to either side The *x ray examination* may not be of help in the diagnosis but sometimes reveals associated changes which by implication point to the possibility A diffuse homogeneous clouding of one pulmonary field unusual in pulmonary tuberculosis alone may suggest suppurative pneumonia and impaired ventilation of the lung or lobe Evidence of obstructive emphysema may be detected and possibly masses of enlarged or calcified lymph node in the mediastinum *Bronchoscopic examination* which if carried out by skilled and experienced operators is safe in these cases reveals the changes described above

The *diagnosis* rests on varying combinations of observations In a patient with tuberculosis of the tracheobronchial lymph nodes demonstrated by x ray but usually not by physical examination bronchoscopic examination may lead to the discovery that erosion of the trachea or bronchus is under way If ulceration has occurred tubercle bacilli may be found in the sputum Conversely if tubercle bacilli are found in the sputum of a patient without cavernous pulmonary tuberculosis the possibility of a tracheal or bronchial lesion is to be suspected and this sometimes is verified by bronchoscopic examination In the case of recognized pulmonary tuberculosis the discovery of the suggestive symptoms and physical signs described above often will lead to the diagnosis of bronchial lesions by bronchoscopic examination In chronic fibroid cases the symptoms may be traced to distortion of the bronchi by the retraction of fibrous tissue without specific endobronchial changes

Treatment — In cases of endobronchial ulcerating lymphadenitis the treatment is directed to the lesion the subsidence of which may be followed by healing of the bronchial ulcer In the case of pulmonary tuberculosis the treatment of the bronchial lesion is indicated by the individual findings Granulations may be reduced by the topical application of silver nitrate in aqueous solution local ulcers may be treated in the same

the pulmonary parenchyma which previously was clear Most of the lesions are small and superficial appearing as localized infiltrations which may slough leaving behind shallow lenticular ulcers surrounded by diffuse reddening and edema of the mucosa These usually are single but may be numerous In other cases the invasion of the tracheal or bronchial wall is deeper leading to marked infiltration more or less fibrosis and sometimes deep ulcers and granulations which may heap up in the form of a localized tumor tuberculous granuloma After healing the bronchial mucosa may be restored or there may be local scars which if extensive lead to stenosis of the canal

Obstructing granulations or stenoses may interfere with normal drainage of the bronchi beyond the point of involvement and this in turn may favor the development of acute or chronic suppurative pneumonic lesions As a consequence the affected part of the lung may become involved in a mixed process Occasionally this mechanism leading to necrosis of the parenchyma is responsible for the breaking down and activation of tuberculous lesions which previously were healed The sudden increase in the size of thin walled cavities in some cases may be due to partial obstruction of the efferent bronchus which causes an inflation of the cavity by its interference with normal ventilation check valve mechanism Similarly obstructive emphysema of one lung may occur In still other cases the persistence of tracheobronchial lesions after the pulmonary lesions have become arrested creates troublesome situations such as a continuing discharge of pus bearing tubercle bacilli which may lead to other complications or a gradually increasing stenosis which may cause dyspnea and other symptoms The symptoms vary according to the extent and location of the lesion

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way Some have tried cod liver oil topically Kernan has devised an applicator for the use of ultraviolet radiation The actual cautery is not often used because of the danger of hemorrhage Kernan has used also the galvanic current to soften superficial scars and to promote the healing of infiltrations In some of these cases if active suppuration is not taking place in the lung artificial pneumothorax has been used with benefit to reduce the motion of the lung as well as the related bronchial lesion The lesions if extensive constitute a serious complication which may prolong the patient s illness and contribute to a permanent disability

TUBERCULOSIS OF THE LARYNX

Tuberculosis of the larynx is found rarely except as a complication of cavernous pulmonary tuberculosis Hematogenous infection has been described but as a clinical development this is certainly uncommon I have not found it in cases of strictly hematogenous tuberculosis and its scarcity among children undoubtedly is due to the fact that they do not often have chronic pulmonary disease Once the larynx has become affected the disease may progress here even after the pulmonary lesions have become arrested but as a rule the two run pari passu The common site of invasion is in the posterior part of the larynx such as the interarytenoid space posterior end of the vocal cord or the mucosa over the arytenoid cartilage The lesions most often are predominantly *unilateral but may be symmetrically bilateral They vary from* a localized tubercle or ulcer of one of these structures to a diffuse exudative lesion involving all the soft tissues of the larynx in which case ulceration may be extensive In some instances inflammatory edema and ulceration of the epiglottis predominates In advanced stages other laryngeal cartilages are attacked Healing may leave behind only a small granuloma a permanent thickening of the interarytenoid mucosa or if particularly extensive stenosis of the glottis

The early symptoms occur in a case of pulmonary tuberculosis in which tubercle bacilli are being or have been discharged from the lungs and consist of intermittent hoarseness or huskiness of the voice which may be noticeable only in the early morning or after a good deal of talking Dryness and tickling in the larynx are common As a rule there is no pain at this stage Laryngoscopic examination shows a slight thickening of the mucosa localized in the posterior part of the larynx and this may be associated with slight redness and possibly beginning ulceration The lesion at this stage often is mistaken for simple catarrhal

laryngitis but the persistence of symptoms beyond a week or so and the presence of pulmonary tuberculosis usually justifies a presumptive diagnosis

In the more advanced stages the patient complains of increasing hoarseness which may be constant and associated with more or less soreness especially on taking irritating food Later particularly when the epiglottis become involved there may be severe dysphagia and regurgitation of liquid food on attempting to swallow The pain becomes severe and persistent and if the inflammatory edema is intense there may be difficulty in breathing Bronchorrhea and salivation may be profuse Bleeding rarely occurs Examination shows extensive and ulcerative changes as described When the cartilages are involved external palpation may elicit tenderness in the structure and the pain during palpation or on swallowing may be referred to one or both ears

Treatment to be successful necessitates alertness to the possibility of laryngeal involvement in pulmonary tuberculosis and routine examination of the larynx as soon as the latter diagnosis is made The enforcement of vocal rest in case any localized redness or swelling is detected in the posterior part of the larynx is most important This is accomplished by having the patient talk only in a labial whisper avoiding any use of the vocal cords and in some cases by complete silence allowing communication only by pad and pencil The inflammation watched by laryngoscopy from week to week usually subsides slowly under this treatment and eventually heals It may be necessary however to continue vocal rest for many weeks or months After ulceration and granulating lesions have developed the use of the actual cautery in the hands of an expert may be most helpful special cautery points being employed for this purpose Such treatments may be repeated at intervals of one or several weeks depending on the response Sometimes the cautery may be used to relieve pain as when the epiglottis is involved extensively Topical applications of various acids and escharotics have been tried but are not as effective as the actual cautery

In severe cases pain and dysphagia may be alleviated by the proper use of a 2 to 4 per cent aqueous spray of cocaine hydrochloride or some other local anesthetic Anesthetization or alcohol injection of the superior laryngeal nerve as it emerges from the larynx may relieve the pain when the involvement is unilateral The needle is inserted through the skin of the neck after ascertaining the landmarks The nerve also has been sectioned through a surgical incision Both nerves may be blocked but pain from epiglottic involvement is not relieved by this procedure alone

Occasionally it is necessary to feed through a nasal tube or a gastrostomy tube Tracheotomy seldom is necessary and then only because of interference with breathing The prognosis is excellent in early cases treated properly which means proper treatment of the pulmonary tuberculosis as well In more advanced cases the prognosis is hopeful also if the treatment is carried out patiently and perseveringly The most unfavorable situation is in acute fulminating cases with severe inflammatory edema and rapid necrosis and ulceration these are associated usually with severe tuberculosis of the lungs and the outlook is poor

Tuberculosis of the Pharynx and Tonsils

The tonsils may be infected by surface contamination or by a blood stream invasion Routine examination of tonsils removed from healthy people have shown as many as 5 per cent harboring tubercles (Pollard and Combs Long Seibert and Gonzalez) These as a rule produce no symptoms and remain isolated and latent When progressive there is a caseous necrosis and ulceration of the tonsils leaving behind ragged greyish yellow ulcers with irregular necrotic edges Invasion of the pharynx may be revealed by the development of isolated or multiple shallow ulcers on the posterior wall these lesions being more frequent in association with tuberculosis of the larynx Another type is represented by extensive involvement of the fauces soft palate and uvula which frequently is associated with ulcerative tuberculosis of the tonsil The soft parts become moderately red edematous and thickly studded with granules which sooner or later take on a yellowish appearance from the caseous necrosis fissure like ulcers develop and gradually extend This miliary like invasion is rare in generalized miliary tuberculosis and to me does not seem to represent a hematogenous process rather a local lymphogenous dissemination

Progressive involvement of the pharynx and tonsils giving rise to clinical symptoms is very uncommon but when it occurs is most distressing The symptoms vary from slight pain on swallowing to intense and constant pain severe dysphagia and profuse salivation Because of the difficulty in eating the patient may rapidly become emaciated The prognosis in cases with isolated shallow ulcers of the posterior pharyngeal wall sometimes is favorable under treatment but extensive infiltrations are most unfavorable and the fatality rate is high

Treatment of localized ulcerous lesions consists in cleansing and the application of the actual cautery point which may encourage healing Direct exposure to the sun or to artificial ultraviolet rays on a graduated

schedule may be helpful In the acute and extensive cases however treatment usually is only palliative consisting of topical application of local anesthetics and sometimes freezing with the carbon dioxide pencil to alleviate pain

TUBERCULOSIS OF THE MIDDLE EAR

Tuberculosis of the middle ear occurs in 5 to 10 per cent of cases of chronic advanced tuberculosis the infection being introduced by purulent discharges arising from pulmonary cavities and gaining access through the eustachian tubes Invasion by way of the blood stream seems to occur much less often After the initial inflammation suppuration frequently follows with perforation of the tympanum Invasion of the mastoid cells to a significant degree is seen seldom Following perforation of the drum granulations may arise and as a rule there is more or less scarring with a chronic discharge Secondary infection with pyogenic organisms is common Permanent deafness of slight or moderate degree is the rule and sometimes the hearing is almost totally lost

Symptoms are rather typical consisting of the development of a painless deafness sometimes associated with tinnitus and a feeling of fullness in the ear The later perforation usually is painless also and the first symptom may be the discovery of a purulent discharge As a rule one ear is involved but both may be affected simultaneously or successively The diagnosis hinges on the recognition of such symptoms in a patient with pulmonary tuberculosis and in the early stage on the finding of a slightly bulging and slightly reddened opaque drum later by the finding of a perforation Tubercle bacilli may be demonstrated in the pus but must be distinguished from nonpathogenic acidfast bacilli from ear wax Conversely such symptomatic and physical findings should lead to further examination for a source in the lung

The *treatment* in unperforated cases is expectant Such a patient should be under treatment for the associated pulmonary tuberculosis The otitis may heal slowly without perforation but not as a rule After perforation has occurred the ear canal is cleansed regularly with irrigations and a pledget of cotton is retained to absorb purulent discharges Mild antiseptics may be used in the irrigations Granulations may be cauterized More active local treatments are seldom of any avail and the process usually settles down to a chronic state which except for the partial deafness does not annoy the patient particularly if the discharge becomes minimal or actually disappears Mastoidectomy seldom is necessary

Tuberculosis of the Nose and Mouth

Tuberculosis of the *nose* is very uncommon The mucosa may be inoculated by a tuberculous patient who picks the nose and in these cases a chronic perforating ulcer of the septum may develop Invasion may occur by extension from lupus of the face Lesions of the paranasal sinuses have been identified but are rare

Tuberculosis of the *tongue lip* and *oral mucosa* is observed occasionally in patients with open pulmonary tuberculosis probably less than one per cent The tongue is involved the most frequently Mucosal invasion may represent an extension from lupus of the face Otherwise infection usually is due to contamination of an abraded area by infected discharges from the lungs The tongue or lip may be scratched by biting or by a rough tooth and the organisms may enter at this point A fissure like ulcer may develop at the corner of the mouth slowly extending or a round ulcer with an indurated base may occur elsewhere on the lips Similarly on the tongue the ulcer first may be superficial shallow and greyish looking usually it is single and located on the margin or near the tip This if it extends is followed by more or less marked tuberculous induration and further sloughing to leave behind round or fissure like ulcers which when spread open reveal granulomatous edges and a greyish yellow necrotic base The mucosal surface and the muscular structure of the tongue may become widely involved with numerous points of caseation and sloughing and moderate swelling and as a rule granulations develop but remain partly hidden by the superficial necrotic membrane Such extensive invasion is seen particularly when the original ulcer is left untreated the prognosis then becomes very serious and death frequently results from this and the associated pulmonary disease

The symptoms depend on the extent of the lesions the first manifestation being slight irritation and soreness Later as the infiltrations and ulcers extend there is exquisite and constant pain and tenderness aggravated by manipulation or attempts to eat Acid or salty food is particularly irritating Bleeding seldom occurs The early diagnosis depends on recognizing a small ulcer which fails to respond rapidly to topical treatment in a patient who is known or found to have pulmonary tuberculosis Tubercle bacilli sometime may be recovered by swabbing or lightly curetting the lesion but the organisms of course may be from the pulmonary cavities The original superficial character of the ulcer the appearance of a caseous necrotic and granulating base and margin and the discovery of the organisms make the diagnosis almost certain Occasionally the question of carcinoma in a tuberculous patient may

have to be considered and a tissue biopsy may be necessary but this is to be avoided if possible since an incision may favor extension of the tuberculous process

Treatment in the early stages consists of the application of the actual cautery sometimes of silver nitrate and the use of heliotherapy applied directly to the lesion with the Kromayer lamp or exposure to the sun s rays More extensive involvement if the process still is localized very occasionally may be an indication for surgical resection but this offers no promise in rapidly progressing cases or when the lesions are diffuse and multiple In such cases the treatment is directed to palliation of the pain and supporting the general resistance

Tuberculosis of the Alimentary Tract

The *esophagus* and *stomach* are involved rarely A tuberculous node in the mediastinum may perforate and empty itself into the esophagus Later a diverticulum may develop at this site and this may result also from retraction of a scar even though the node has not actually perforated Rare isolated tuberculous ulcers of the gastric mucosa have been reported in pulmonary cases and in other instances the stomach has been involved by invasion from lesions in adjacent structures such as the lymph nodes I have never been able to make the diagnosis clinically and have seen only one questionable case of tuberculous ulcer of the stomach at autopsy

Tuberculous *enteritis* or *enterocolitis* is one of the more common complications of pulmonary tuberculosis the incidence was slightly over 50 per cent in the 1 116 autopsied cases of Perla and Biller It is seen seldom except in the presence of the latter Infection therefore may be assumed to occur most often by a surface contamination with discharges raised from pulmonary cavities and swallowed Any part of the smaller or large intestine may be involved but the common site is in the lower half of the jejunum ileum and cecum the appendix may participate Lesions appear as infiltrations of the intestinal mucosa and lymphoid tissue which may soon go on to necrosis and ulceration The ulcers are shallow and may have a heaped up granulomatous margin and a red inflamed base They may be single or numerous varying in size from a microscopic erosion to an almost complete denudation of lengthy sections of the gut The layers of the intestine may be deeply infected and there may be a localized fibrinous miliary or infiltrative reaction of the overlying visceral peritoneum Perforation sometimes occurs but is very uncommon in relation to the frequency of observed ulcers usually it is a

preterminal event Healing may occur leaving slightly retracted scars or the process may become localized as in the cecum and go on to a chronic granulomatous inflammation with hyperplasia of the intestinal wall gradual narrowing of the lumen and eventually, obstruction Along with this there may be chronic localized peritonitis

The symptoms at first are vague entirely lacking or represented merely by a change in bowel habits such as slight occasional diarrhea As the involvement becomes extensive the patient experiences cramp like lower abdominal pain particularly on eating and may have severe diarrhea seldom bloody In the early cases constitutional symptoms are loss of weight and fatigue out of proportion to the extent of the pulmonary involvement Secondary anemia is common In the advanced stages the intestinal lesion contributes to the marked wasting of the soft tissues The diagnosis is suggested strongly by such symptoms in a patient with pulmonary tuberculosis Examination of the abdomen usually is quite negative although in chronic cases a mass may be felt in the right lower quadrant Studies of the blood are not very helpful Tubercle bacilli may be cultivated from the feces but this finding usually is not of value since most of the patients have a positive sputum X ray examination after the barium meal or enema or double contrast enema and air inflation shows filling defects and spasm in the ileocecal region and hypermotility of the intestine This is the most dependable single examination and while its reliability is not absolute it is very helpful in experienced hands

Treatment consists of general measures which are already usually in force for the pulmonary tuberculosis the use of a bland low residue diet during the active phases and sometimes after their subsidence and in some cases the use of artificial heliotherapy Some believe the latter has a particularly good effect in intestinal tuberculosis but in my experience the most important thing is the regulation of the diet (See chapter of the author in Pattee s *Practical Dietetics*) To control severe symptoms it may be helpful to limit the intake to four or five ounces of boiled skimmed milk and a little dry toast or cracker every three to four hours until relief is obtained This followed out for one to three days may give great alleviation the bland diet then being gradually built up Fresh fruits fruit juices and fat in large amounts is not well tolerated by these patients and vitamines may have to be supplied in concentrated form Paregoric bismuth and opium powders perorally or calcium gluconate intravenously may be helpful in relieving intestinal pain Surgery is not indicated except in the localized hyperplastic type of disease where there is beginning intestinal obstruction In these cases the infected part of

the bowel may have to be resected See also Intestinal Tuberculosis in Chapt IV Vol III

Tuberculosis of the *rectum* is uncommon and when it occurs usually is found in a patient with pulmonary tuberculosis and in whom other sections of the bowel are involved The ulcerating lesion may become chronic and lead to gradual obstructive constriction Lesions of the perianal and perirectal tissues as a rule are ascribable to a similar mechanism of infection the resulting abscess usually ruptures externally but it may perforate the rectum also Abscesses in this region should be regarded with suspicion of a tuberculous etiology if the patient has pulmonary tuberculosis this may be confirmed by the finding of bacilli in the aspirated pus or by curettings from the abscess which has drained to the outside The sinus or fistulous tracts may show a tendency to heal spontaneously but they frequently become chronic with a small purulent discharge and eventually have to be treated surgically

Tuberculosis of the Lymph Nodes

Lesions in the lymph nodes are observed frequently after tuberculous infection in fact it may be said that this is almost inevitable After the primary infection which usually is in the lung the regional nodes at the hilum are affected and other tributary nodes then may become involved progressively Multiple localizations including the superficial nodes are seen where the infection has become disseminated through the blood stream Wherever the transported bacilli settle out from the systemic circulation they may be engulfed in phagocytes and carried into the lymphatic system this constantly operating mechanism accounts for widely scattered lymphadenitis observed in cases of subacute and chronic hematogenous tuberculosis (lymph nodes of the mediastinum mesentery head epitrochlear axillary and inguinal regions etc)

Following the lymphoid hyperplasia and tubercle formation changes vary from hypertrophy and caseation to chronic granulomatous lesions which finally may become latent and stabilized Eventually calcareous infiltrations may appear in any caseous nodes these are found most often in the tracheobronchial group less frequently in the cervical and retroperitoneal chains Progressive lesions result in colliquative necrosis and often in sloughing into or through adjacent tissues particularly when these are superficial Tuberculous periadenitis with the agglutination of different nodes and infiltration of contiguous structures is observed commonly All these lesions make up a picture once commonly known as scrofula or the King s Evil Considering the frequent infection of

preterminal event Healing may occur, leaving slightly retracted scars or the process may become localized as in the cecum and go on to a chronic granulomatous inflammation with hyperplasia of the intestinal wall gradual narrowing of the lumen and eventually, obstruction Along with this there may be chronic localized peritonitis

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persist during weeks or months The nature of the fever may seem obscure until the lymphatic involvement is identified This is particularly true when numerous superficial lymph nodes slowly become enlarged When the lesions are limited as in the neck the differential diagnosis usually is not difficult since acute lymphadenopathies of other nature most often are clearly related to inflammations of the nose ear or throat and subside quickly or go on to acute suppuration Other conditions to be distinguished particularly when the involvement is more generalized include Hodgkin s lymphoblastoma lymphosarcoma metastatic neoplasms and acute or subacute generalized infections Complete and careful examination must include a study of the cytology serology and bacteriology of the blood observation of the clinical course particularly to detect the development of specific lesions and eventually in some cases a biopsy of a superficial node In situations where the lesions may possibly resemble tuberculosis as in syphilis it may be necessary to inoculate an animal with the tissue

The *treatment* of tuberculous lymphadenitis is at the start conservative because of the great tendency for these lesions to heal spontaneously Since the early arrest of the inflammation is to be greatly desired usually it is wise to give these patients a period of bed rest In young people particularly the desirability of rest treatment for a few weeks or months depending on the individual situation is to be stressed Because of the less serious potentialities this usually need not be as strict as in the case of pulmonary tuberculosis but the same principles should be observed and the patient s routine of activity should be supervised carefully for one to two years particularly if he is a youth This will accomplish much in avoiding the potentialities of further lympho hematogenous disseminations

After the lesions have become quiescent tonic measures such as general heliotherapy started with small doses and gradually increased may be of advantage Tuberculin was once popular for the treatment of this condition but is of dubious value because of the difficulty in avoiding reactions which might prove serious The same thing may be said of x ray therapy although some success has been reported in reducing the swelling in chronic cases It is to be avoided in tuberculosis of the internal lymph nodes particularly tracheobronchial lymphadenitis because of the possibility of inducing further caseous necrosis and dissemination through the blood stream

Surgical treatment sometimes is indicated in the case of superficial adenopathies because of the size of the mass and the tendency to progressive caseation and liquefaction but as a rule careful observation over

the lymphatics however one is impressed by their resistance and the tendency of the lesions to heal Old latent foci may become active from time to time but the general tendency is toward permanent quiescence

The local symptoms depend on the site and extent of the group involved In the cervical region the nodes of the upper chains are affected most commonly The patient notices lumps growing in his neck which may be slightly sore and tender or quite painless The growth may be almost imperceptible and eventually the process may come to arrest with only a single node involved or the whole chain may participate Occasionally the enlargement is rapid, progressive and quite painful particularly on motion of the neck The enlargement may extend as a collar from the ear around to the midline in front or perhaps encircle the neck in front of both ears The appearance resembles that of a hog s neck and according to Henning originally may have suggested the designation scrofula (Latin *scrofulæ* diminutive of *scrofa* a breeding sow) The size of the mass may tilt the head to the opposite side may displace the trachea and limit motion of the neck because of the tenderness At any point the lesions may become stationary and then subside so that only small isolated enlargements remain When softening occurs this becomes evident on palpation by the finding of fluctuating areas in the middle of the individual nodes If these are superficial and become adherent to the skin the latter becomes red and shiny and gradually thinned out until perforation occurs A gradual discharge follows or considerable pus may be expelled containing round lumps which resemble necrotic casts of the nodes There may be extensive undermining leading to multiple sinuses surrounded by areas of atrophic partially scarred and bluish appearing skin Similar changes may be observed in other locations such as the axilla and groin

The local manifestations in the case of mediastinal mesenteric or retroperitoneal involvement are less distinctive The behavior of tracheobronchial lymphadenitis has been discussed in the paragraph on Tuberculosis in Children Mesenteric or retroperitoneal lymphadenitis tabes mesenterica may if extensive give rise to vague abdominal pains and to palpable masses In the thorax ulceration into the trachea or bronchus the esophagus pericardium or the heart may lead to striking clinical pictures some of which have been described In the abdomen one of the hollow viscera may be perforated by a sloughing node or the peritoneum may be infected

The constitutional symptoms do not differ from those of any other tuberculous toxemia The loss of weight fatigue and afternoon fever are not usually so pronounced as in tuberculosis of the lungs but may

The infection originally is hematogenous but this may have occurred many months or years previous to the appearance of symptoms the lesion meanwhile having remained latent After any acute inflammatory reaction has subsided the thickened and nodular epididymis remains palpable and slightly tender and similar changes may be found in the *vas deferens*

The *testicle* occasionally becomes involved and the process then may continue as a slowly progressive caseous necrosis with agglutination of the scrotal membranes abscess formation and eventually sloughing through the skin with formation of sinus tracts The further course then may be progressive or this may be interrupted by periods of quiescence and partial healing Occasionally chronic lesions continue their indolent course for many months with a resultant gradual destruction and atrophy of the testicle

Extension along or through the vas may lead to involvement of the *seminal vesicles* and *bladder* In the latter case the symptoms of vesical irritability and inflammation then develop Eventually both epididymes may become involved very occasionally this is the case from the very start According to Schleussing simultaneous involvement of the genital and urinary tract are more common in the male (5- per cent) than in the female (9 per cent) although the incidence of urinary tuberculosis is the same in both sexes The prognosi generally is unfavorable for healing of genital tuberculosis in the male without surgical intervention although when the lesion is small and localized it may become arrested spontaneously and permanently In progressive cases the possibility of lymphohematogenous disseminations from the genital focus must be considered although fatalities of this nature are observed in only a small minority of the cases

Treatment of tuberculosis of the male genitalia during the acute phases is conservative the patient being kept in bed and the scrotum supported by a suspensory or other suitable device The application of an ice bag may relieve the pain and tenderness As a rule the acute inflammation gradually subsides during one week to a month and scrotal effusion if any becomes absorbed During the quiescent phase or if the lesion is only slowly progressive resection of the epididymis and of the testicle if this is involved usually is indicated In advanced cases the possibility of resection of the entire seminal tract is to be considered

Tuberculosis of the *penis* is rare Ulcerating lesions of the glans may result from the inoculation of abraded surfaces with tubercle bacilli carried on the hands if the patient has a positive sputum Granulomatous lesions of the shaft have been observed but are very rare

a period of time will determine first whether satisfactory healing can be expected without this intervention Sinus tracts are treated with helio therapy and various surgical measures depending on the extent and location

TUBERCULOSIS OF THE GENITAL ORGANS

In women the most common site of invasion is the *fallopian tubes* and this may be traced to lympho hematogenous dissemination from a distant or direct extension from some adjacent lesion e g , tuberculous peritonitis One or both tubes may become infiltrated, and while it may be self limited the process often goes on to caseation and extension to the surrounding structures so that localized or diffuse peritonitis is a potential complication The symptoms are those of tuberculous toxemia augmented by lesions in other parts of the body Local symptoms usually are vague and passing consisting of occasional slight pain in the lower abdomen and possibly amenorrhea and leucorrhea which, as a rule is not very profuse Abdominal and pelvic examinations may disclose thickening and tenderness of the adnexa and the sausage shaped mass of the involved tube Tubercle bacilli seldom may be discovered in the vaginal discharge If conservative rest treatment does not suffice laparotomy and resection are indicated, and this is favored by some to prevent or cure secondary peritonitis

Tuberculosis of the *ovary* is a fairly frequent accompaniment of tuberculous salpingitis but the ovarian involvement usually is not severe The *uterus* is not often infected Extension from the fallopian tube or hematogenous invasion may occur with invasion of the endometrium Collins has stressed the importance of the diagnosis and surgical treatment of tuberculosis of the *cervix* Involvement of the *vagina* and *labia* is rare The diagnosis is made by observing usually in a patient with other tuberculosis granulomatous and ulcerating lesions from which tubercle bacilli are obtained Culture and animal inoculation may be necessary to identify the true nature of the organisms Occasionally examination of tissue secured by biopsy may be indicated

In the male the site of the first tuberculous invasion may be difficult to determine Usually a lesion of the *epididymis* is the first to be identified clinically but autopsy studies such as those of Perla and Biller indicate that in most cases the *prostate* is involved first A diffuse thickening or localized nodular lesion may be detected in the epididymis and this may be associated with a very acute perifocal inflammatory reaction with swelling of the surrounding tissues and serous effusion in the scrotum

The infection originally is hematogenous but this may have occurred many months or years previous to the appearance of symptoms the lesion meanwhile having remained latent After any acute inflammatory reaction has subsided the thickened and nodular epididymis remains palpable and slightly tender and similar changes may be found in the *vas deferens*

The *testicle* occasionally becomes involved and the process then may continue as a slowly progressive caseous necrosis with agglutination of the scrotal membranes abscess formation and eventually sloughing through the skin with formation of sinus tracts The further course then may be progressive or this may be interrupted by periods of quiescence and partial healing Occasionally chronic lesions continue their indolent course for many months with a resultant gradual destruction and atrophy of the testicle

Extension along or through the vas may lead to involvement of the *seminal vesicles* and *bladder* In the latter case the symptoms of vesical irritability and inflammation then develop Eventually both epididymes may become involved very occasionally this is the case from the very start According to Schleussing simultaneous involvement of the genital and urinary tract are more common in the male (52 per cent) than in the female (9 per cent) although the incidence of urinary tuberculosis is the same in both sexes The prognosis generally is unfavorable for healing of genital tuberculosis in the male without surgical intervention although when the lesion is small and localized it may become arrested spontaneously and permanently In progressive cases the possibility of lymphohematogenous disseminations from the genital focus must be considered although fatalities of this nature are observed in only a small minority of the cases

Treatment of tuberculosis of the male genitalia during the acute phases is conservative the patient being kept in bed and the scrotum supported by a suspensory or other suitable device The application of an ice bag may relieve the pain and tenderness As a rule the acute inflammation gradually subsides during one week to a month and scrotal effusion if any becomes absorbed During the quiescent phase or if the lesion is only slowly progressive resection of the epididymis and of the testicle if this is involved usually is indicated In advanced cases the possibility of resection of the entire seminal tract is to be considered

Tuberculosis of the *penis* is rare Ulcerating lesions of the glans may result from the inoculation of abraded surfaces with tubercle bacilli carried on the hands if the patient has a positive sputum Granulomatous lesions of the shaft have been observed but are very rare

Tuberculosis of the Urinary Tract

Initial infection of the kidney is with few exceptions by way of the blood stream At autopsy small renal tubercles are found frequently the incidence being reported to vary from 20 to more than 60 per cent in cases of pulmonary or hematogenous tuberculosis Gross involvement however was found postmortem by Perla and Biller in only 8 per cent of 1 116 cases of pulmonary tuberculosis after the age of fifteen The implication is that most renal lesions do not progress to produce destruction of the organ with clinical symptoms When progression occurs a focus usually in the cortex spreads into the pyramids which are relatively vulnerable following necrosis fistulous tracts form leading into the renal pelvis which in time may become involved Extension to adjacent pyramids may follow and eventually large sections of the kidney or even the whole organ may become involved The kidney may be widely excavated or may be transformed into a mass of caseous matter which in time may be infiltrated with calcium salts The ureter is relatively resistant but in protracted cases may become infiltrated widened scarred and possibly ulcerated With scarring and occlusion of the ureter the diseased kidney may become sealed off Infection of the bladder is due to the transportation of bacilli in the urine from the involved kidney and is a rather frequent complication

Tuberculous involvement of a diffuse or nodular character appears first around the ureteral orifice and in time ulceration may develop Continuation of the infection leads to extensive involvement of the entire bladder wall and occasionally this may become replaced with granulation and fibrous tissue leading to shrinkage and great reduction of the vesical capacity Calcification of the wall has been observed but is rare The alteration of the opposite ureteral orifice may permit a reflux of infected urine resulting in progressive lesions in the remaining kidney Extensions to the male genital tract also may occur The possibility of spontaneous healing of renal tubercles is to be considered and from autopsy findings would seem to be fairly frequent in the case of small or miliary lesions Once a caseous lesion has developed however healing is regarded generally as a rare possibility

Symptoms —Tuberculosis of the kidney may exist for years without giving rise to manifestations of which the patient is aware and there may be little or no impairment of the general condition as long as only one kidney is involved While pain occurs at some time in a majority of the cases this may not bring the patient to the physician Most often the pain is dull and aching sometimes it is colicky due to the passage of

clots or broken down tissue through the ureter It may be confined to the lumbar region on one side or at times referred to the lower abdomen or to the testicle

The discomfort which is most arresting however is that due to involvement of the bladder This may cause a burning discomfort in the pelvis urinary frequency dysuria and even strangury Gross hematuria occurs in many cases depending on the duration of the disease Frequently it is an early symptom in fact it may be the first one recognized by the patient Occasionally free blood is passed but as a rule the urine is only cloudy In other cases the patient may first suspect trouble when he notices turbidity of the urine pyuria

Constitutional symptoms are not often striking in the early stages but as the disease progresses fever loss of weight fatigue and eventually even emaciation may appear In long standing cases in which there has been considerable renal destruction and perhaps ureterostenosis symptoms of nitrogen retention and eventually uremia develop However few survive this long It may be repeated that tuberculosis of the bladder may be secondary also to lesions in the male genital tract and that its presence is therefore not necessarily an indication of renal involvement In this event extension to the kidney may be due eventually to a reflex of infected urine

The *diagnosis* of tuberculosis of the urinary tract depends first on a recognition of suggestive or definite symptoms The possibility should be further investigated under any of the following conditions emphasized by Herbst (1) unilateral renal infection (2) hematuria with no obvious explanation (3) pyuria with no organisms demonstrable by ordinary staining methods (4) persistent pyuria of any kind (5) cystitis which does not respond to a reasonable period of treatment (6) pyuria or dysuria in individuals with a history of tuberculosis or active extraurinary tuberculous lesions nodular lesions in the seminal tract

Physical examination may reveal slight tenderness in the upper lumbar region but this sign is not to be expected in very early cases Tenderness over the bladder likewise usually is a sign of extensive involvement and in advanced cases a thickened ureter sometimes is felt on vaginal or rectal examination Proper examination of the urine is very important An unusual number of red blood cells or of any pus cell should lead to further investigation unless these otherwise are explained readily Albumin may be found usually in small amounts A thorough search for tubercle bacilli is made At least 200 c c of urine are collected and centrifuged at high speed the specimens from several centrifuged tubes should then be collected in one tube and centrifuged again This is examined micro

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year cure was 50 3 per cent and the chance of being either cured or improved was 75 2 per cent However if the guinea pig was positive the patient s chance of dying within five years increased to 41 8 per cent and the chance of a five year cure dropped to 21 8 per cent

Following nephrectomy secondary lesions of the bladder and ureter if not very extensive usually heal occasionally the urethral stump has to be treated further See also Tuberculosis of the Urinary Tract in Chapter XII-A in Vol III

Tuberculosis of the Central Nervous System

Localized infections may occur by bacilli carried in small numbers from a distant focus such as a mediastinal lymph node through the blood stream Single or multiple tubercles may develop in the substance of the brain or spinal cord more often in the former Small tubercles conceivably may heal but experience indicates that probably most of them keep growing The clinical picture may be that of a brain tumor usually of the cerebral cortex less often of the cerebellum or spinal cord In rare cases the caseous tubercle may become calcareous and identifiable in the roentgenograph In most cases the meninges eventually become involved Meningitis therefore may represent a development from such a previously established local le ion or may be a part of acutely disseminated tuberculosis The greater frequency of such disseminations in early life accounts for the higher incidence of tuberculous meningitis in young children As a terminal complication of chronic pulmonary tuberculosis in adults it occurs in 5 to 7 per cent of the cases

In a child the prodromal symptoms are irritability fatigue fretfulness anorexia and low fever An adult however usually complains of persistent headache followed by these other manifestations The persistence and gradual increase of the symptoms the development of stiffness of the neck photophobia and neurological signs such as strabismus muscular twitching and other signs of meningeal irritation suggest the diagnosis Neurological examination reveals rather constantly rigidity of the neck a positive Kernig sign and usually other significant deviations also Spinal paracentesis yields fluid under more or less pressure the examination of which usually confirms the diagnosis (See also Tuberculous Meningitis in Volume VI Chapt XIII)

Generalized Lympho hematogenous Forms of Tuberculosis

Acute generalized miliary tuberculosis is seen most often in infants or young children and results from a sudden overwhelming invasion of the

scopically and whether or not acidfast bacilli are found the remaining sediment should be cultured or inoculated into guinea pigs In this way an early ulcerative lesion is not likely to escape diagnosis

The possibility of excretory bacilluria that is, the excretion of tubercle bacilli from the blood stream through a normal kidney sometimes is suggested to explain the laboratory finding of organisms in the urine of an apparently healthy patient There is very strong evidence accepted by a great majority of observers that such a phenomenon does not occur, but rather that there is a background at least of microscopic tubercles in the kidneys to account for it In view of the fact that early renal lesions may be asymptomatic it is obligatory therefore to conclude that the demonstration of tubercle bacilli in the urine is evidence of a lesion The demonstration of excretory bacilluria in the case of animals infected experimentally by way of the blood stream does not invalidate this principle

Urography with the use of suitable opaque solutions is depended upon to confirm the diagnosis The chief positive findings are defects indicating destruction of renal tissue deformation of the calices and widening of the ureter Occasionally the roentgenograph shows the densities of tuberculous calcifications The tendency of some (Emmett and Braasch) is to dispense with retrograde pyelograms and to rely on excretory urograms and examination of the ureteral specimens of urine from the good kidney It is considered advisable to keep cystoscopy at an absolute minimum to save the patient discomfort and possible harm Cystoscopy of course usually is performed at least once to secure the ureteral specimen of urine and to visualize changes which may have occurred in the bladder

Treatment — Conservative rest treatment may be followed by healing of minute renal lesions but is not relied upon by most experienced physicians In cases of extensive bilateral renal disease this may be the only recourse The preferred treatment is nephrectomy and this should be done early in order to attempt to prevent involvement of the bladder and the opposite kidney Unilateral nephrectomy sometimes is carried out also in bilateral cases if the better kidney is not too extensively involved The prognosis in varying conditions has been analyzed at the Mayo Clinic by Emmett and Kibler They have had the following experience with reference to the good kidney In cases in which there was a negative urine obtained by ureteral catheterization from the good kidney the patients had a 43 5 per cent chance of a five year cure a 65 2 per cent chance of being cured or improved in that period and only a 20 3 per cent chance of death within five years if tubercle bacilli were not demonstrated by staining or guinea pig inoculation the chance of dying within five years dropped to 13 3 per cent, the chance of a five

so in diameter Because of the long course there is opportunity not only for such caseation but also for ulceration so that the lesions distributed in both lungs may have time to break down into cavities of greater or less extent

Likewise in the subacute cases caseous adenopathies superficially and particularly in the mediastinum and abdomen are frequent as are serous pleural pericardial and peritoneal effusions single or in combination The course of the disease may run for six months or longer and may even become arrested for considerable periods of time but because of the caseous character of the lesions exacerbations are likely to occur and even tually fatality is the rule The symptoms are manifold depending on the rate of development and the nature of the local lesions Subacute dis seminated tuberculosis however is to be suspected particularly in negroes and children who have protracted obscure low moderate or high fevers with generalized lymphadenopathies and effusions in the serous cavities

Chronic disseminated hematogenous tuberculosis is somewhat less common and seems to represent lympho hematogenous infection with small doses of bacilli the resulting lesions becoming arrested because of this factor or the patient s high resistance These chronic forms are observed in older children and in some adults The lesions usually are small dis crete and scattered more or less sparsely in the viscera especially in the lungs where they may be distributed rather symmetrically with a pre dominance at the apices The symptoms are often very vague and repre sented by a chronic state of undernutrition and easy fatigue occasionally persistent or recurring low fever There may be no localizing symptoms unless the lesions have progressed at some point In the lungs the gener alized interstitial fibrosis residual of healing may lead to gradually increasing emphysema and dyspnea which because of its insidious de velopment may not be apparent to the patient

Examination may show no superficial abnormalities and only the signs of emphysema perhaps with a few small rales scattered in the upper one third of one or both lungs The roentgenograph of the lungs reveals a picture which is rather characteristic of scattered predominantly apical or perihilar small sharply circumscribed nodular densities varying in size from a millet seed to four or five mm in diameter rarely larger Some of these may be so dense as to represent small nodular calcifications Similar calcifications in the spleen are demonstrated occasionally by x ray Associated pleural and emphysematous changes may be in evidence A study of the blood may show no abnormal deviations or perhaps a func tional polycythemia The prognosis of this form of tuberculosis is not too bad With proper supervision the patient may live many years perhaps

blood stream from some preexisting focus This may be an ulcerating focus in the lung or elsewhere but usually a caseous lymph node in the abdomen or mediastinum more often the latter Miliary tubercles develop throughout the body the parts favored being the lungs serous membranes liver spleen kidneys and meninges Numerically the lesions may predominate in certain parts, the lungs frequently receiving the brunt of the attack On the other hand the meningitis may be most prominent clinically because of the local inflammation and tensions created in the cerebrospinal canal Since the acute course is cut short by death the tubercles remain small and grey and usually show very little central caseation If the patient has had preexisting clinical tuberculosis the initial symptoms are merely those of a febrile exacerbation but otherwise the patient previously apparently healthy may fall ill with a rapidly developing or acute fever which rises to 103° F to 105° F daily The symptoms then are those of progressive and severe general toxemia with increasing prostration rapid loss of weight and continuing daily fever

The development of meningeal symptoms may direct attention to this localization while a predominant pulmonary involvement leads to gradually increasing dyspnea occasional dry hacking cough with a slight or moderate amount of mucoid expectoration a sense of fullness in the chest and increasing cyanosis There is often profuse sweating especially at night Involvement of the serous membranes may lead to effusions in one or all of the cavities and the symptoms of these may predominate The abdomen may become swollen and distended or the patient may develop increasing dyspnea tachycardia cyanosis and engorgement of the veins of the neck from the tamponade of a pericardial effusion Sometimes small lymphadenopathies are noticed superficially In only a minority of the cases does the spleen become palpable Rarely tuberculides of the skin develop The downhill course continues with the possible variations mentioned until the patient dies at the end of six to eight weeks The prognosis is uniformly hopeless and treatment unavailing

Subacute and chronic hematogenous disseminations are not uncommon in tuberculosis and likewise occur more often in children and in negroes The event however is not rare at any age In the subacute or protracted forms the presumption is that the number of bacilli escaping into the blood stream is not immediately overwhelming and that in some cases there may be a continuous or intermittent seeding of small doses Consequently the disseminated lesions are not uniform as in the case of acute generalized miliary tuberculosis but vary in size and character In the lymph nodes lungs spleen liver kidneys and other tissues tubercles may be seen varying from grey miliary nodules to caseous foci a centimeter or

fection with virulent tubercle bacilli but the effect in human subjects is questioned by many observers Levine and his associates point out the difficulty of drawing conclusions except by a long study and the weighing of many factors Various workers have suggested that attenuated bacilli might regain their virulence in the human body and on account of his success in reestablishing virulence by animal passage Smithburn again raises the point and suggests that unless such potential change can be ruled out the injection of attenuated living bacilli be confined to the practices of animal experimentation Renewed investigations of the possibility of inducing partial immunity with dead tubercle bacilli have been reported recently by Freund and Opie Kinghorn and Dworski also have had some success with vaccine made from sterile caseous material

The most promising practical means of prevention now available is that which guards against the transmission of the infection mainly from the open pulmonary case to others with whom such patient may come in contact This implies early diagnosis preferably before the pulmonary lesion has ulcerated and emphasizes further the desirability of case finding surveys to achieve this end The efficiency and application of available methods has been discussed widely in literature and is becoming well known (Plunkett Edwards Ulrici) The prompt separation of infectious cases especially from those in intimate contact in the home is most important since otherwise the organisms are almost invariably transmitted Another vital factor is the application of treatment of the infectious case sufficient to render the sputum negative for tubercle bacilli if this is at all possible Otherwise permanent supervision and segregation of the patient may be necessary Since advancing age seems to bring with it an increasing native resistance against tuberculous disease the importance of preventing the infection of children is obvious This would not only obviate immediate disaster but also go a long way toward avoiding the exacerbation of latent lesions and endogenous reinfections in later years

In countries where bovine tuberculosis still prevails the example of the United States should be emulated in order to eliminate this source of infection

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with increasing functional embarrassment from the fibrosis and emphysema In some the pulmonary lesions break down and lead to progressive cavernous tuberculosis and its direct complications or ulcerating renal lesions may appear The treatment is designed to build up and preserve the patient s general resistance A period of rest cure perhaps in bed at first may be indicated as well as a permanent limitation of the patient s physical activities and the adoption of a suitable daily hygienic routine Collapse therapy, as a rule, is not indicated unless cavitary lesions develop

Among the chronic hematogenous forms of tuberculosis the place of certain atypical lesions has to be considered There is still disagreement as to whether the lesions coming within the class described as Boeck s sarcoid (see also Chapt I–B Vol IV) are tuberculous or not Pathologically the lesions which may be widely disseminated in the skin eyes lymphatic system bones lungs and other structures are atypical in that the granulomatous changes are not found associated with caseation and tubercle bacilli seldom are demonstrated Clinically the disease is atypical because of its slow development and progression often with the tendency to heal by fibrosis and the absence of caseous or ulcerating lesions in the lungs Nevertheless the granulomatous and fibroid lesions of the lungs usually cannot be distinguished from those of proved chronic hematogenous tuberculosis Occasionally these patients develop definite pulmonary tuberculosis which may be interpreted as a further development from the existing lesions or as a complicating infection of different nature Various aspects of this interesting disease which so closely resembles lymphohematogenous tuberculosis have been considered at length by Longcope, Snapper and Pompen Pinner and others

Prevention of Tuberculosis

Ever since the discovery of the tubercle bacillus it has been the hope that some method of vaccination might be developed which would be sufficient to confer immunity Numerous attempts have been made but none with wholly convincing results The best known method of recent years has been with Calmette s B C G (Bacillus Calmette Guerin) This has been widely used at first perorally but more recently parenterally in many countries Human beings or animals inoculated with this vaccine which is a living attenuated strain of tubercle bacilli usually develop hypersensitivity of the tissues as determined by the tuberculin test, but in some this is evanescent The degree of relative immunity conferred upon animals is influential in helping to prevent or limit subsequent in

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CHAPTER XII-A

SURGICAL TREATMENT OF PULMONARY TUBERCULOSIS

By JOHN ALEXANDER

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INTRODUCTION

Two general types of surgical operations are used in the treatment of pulmonary tuberculosis (1) Those operations that act indirectly upon the affected lung by collapsing it in varying degree are included in the term collapse therapy, which is the form of surgical treatment most extensively used (2) Those operations that directly involve the lung either by removal of the diseased portion or by drainage of tuberculous cavities within it these operations are used relatively infrequently (3) Bronchoscopy although not strictly a surgical procedure has become an integral part of the diagnostic and therapeutic management of many patients with pulmonary disease possibly to receive surgical treatments

The surgical treatment of pulmonary tuberculosis is not a substitute for the hygienic regimen and the close medical supervision that are the essential elements of sanatorium treatment. Collapse therapy, however, by mechanically closing cavities by collapsing and resting the noncavernous lesions and by favorably altering the respiratory physiology frequently accomplishes what the sanatorium regimen alone is unable to do. While surgery places the sanatorium patient in a position to bring about complete healing of the lesions, it does not in itself increase his specific resistance to tuberculosis. This the sanatorium type of regimen does admirably. It follows therefore that a patient who does not accept sanatorium treatment for a sufficiently long time following an operation that has been mechanically perfect in its effect upon the lesions is in danger of suffering a return of active tuberculous disease because the factors concerned in the inadequate resistance to tuberculosis that produced the original illness are likely, unless neutralized, to continue to operate.

The interdependence of the sanatorium and surgery is now recognized universally. In 1931 about 10 per cent of all sanatorium patients in the United States were given some form of collapse therapy; in 1943 the sanatorium use of collapse therapy probably had risen to 50 per cent. Today in a number of the leading sanatoria in which the surgical program has been highly developed 80 per cent or more of all the patients are given surgical treatment. Surgery now is widely considered as indispensable in the management of pulmonary tuberculosis. It is an interesting fact that in those sanatoria in which the choice of the different operations for the individual patients is made expertly and in which the operations are performed expertly the results are so good that it is unusual for a patient to refuse any recommended operation. When the choice and performance of the operations are not expert the results are proportionately inferior.

The distinction made in the last paragraph between expert and inexpert surgical treatment is perhaps obvious, but it is often overlooked by those who according to their personal experiences unduly praise or unduly condemn collapse therapy or some particular operation. Although the surgical treatment of pulmonary tuberculosis is more than fifty years old, its use on a large scale is scarcely ten years old. It is not surprising therefore that sufficient specialized medical and surgical experience and expertness have not yet accumulated to make possible a uniformly high standard of work and clinical results. Until this time comes the surgical treatment of pulmonary tuberculosis will not of course produce its maximal effect upon the lowering of the incidence and death rate of tuberculosis in the population at large. There is no direct measure that can be used to appraise the proportionate share that surgery thus far has had in the continued lowering of the tuberculosis death rate, which began before surgery was used widely and which is, of course, due to many factors. The very large

number of patients whose lives have been saved by surgery and who have been returned to their communities without tubercle bacilli in their sputum and able to resume a gainful occupation obviously have had an important direct influence upon the war against tuberculosis

Indications and Contraindications

The value of surgery is so great that the case of virtually every patient with active tuberculosis should be considered in a consultation between the attending internist and a thoracic surgeon in which consultation all available data should be considered and the x ray films that have been made since the beginning of the illness carefully studied Needless to say the primary consideration should be whether the operative procedure considered most suitable for the particular patient is more likely to help him or because of possible surgical complications to harm him The answer to this question must be based largely upon (1) the attending internist s knowledge of the past behavior of the particular patient s tuberculosis and his estimate of the disease s probable future course if not treated surgically and (2) the particular surgeon s experience and results in similar cases

It is well known that sanatorium treatment unaided by surgery brings about complete healing in a large proportion of patients admitted with minimal tuberculosis* in a partially satisfactory proportion of those with moderately advanced tuberculosis* and in a few with far advanced tuberculosis* At present the stage of advancement of the tuberculosis in patients admitted to the sanatoria of this country is approximately as follows minimal 15 per cent moderately advanced 30 per cent far advanced 55 per cent

Since unaided sanatorium treatment may bring about complete healing some physicians prefer not to use surgery immediately even if there is an apparent pathologico-anatomical indication for a particular operation but instead to observe the behavior of the patient and his lesions during a variable period of

In 1940 the National Tuberculosis Association announced the following definitions in a pamphlet entitled Diagnostic Standard and Classification of Tuberculosis

Minimal — Slight lesions without demonstrable excavation confined to a small part of one or both lungs The total extent of the lesions regardless of distribution shall not exceed the equivalent of the volume of lung tissue which lies above the second chondrosternal junction and the spine of the fourth or body of the fifth thoracic vertebra on one side

Moderately Advanced — One or both lungs may be involved but the total extent of the lesions shall not exceed the following limits

Slight disseminated lesions which may extend through not more than the volume of one lung or the equivalent of this in both lungs

Dense and confluent lesions which may extend through not more than the equivalent of one third the volume of one lung

Any gradation within the above limits

Total diameter of cavities if present estimated not to exceed 4 cm

Far Advanced — Lesions more extensive than Moderately Advanced

unaided sanatorium treatment and to use surgery only if it is finally proved to be necessary This procedure has the advantages of sparing the patient a possibly unnecessary operation and of indicating to the internist the extent to which the patient possesses or lacks an inherent ability to heal his lesions The disadvantages of the plan are (1) Experience has shown repeatedly that initial encouraging improvement often causes the internist to persist indefinitely with the same treatment in the hope that complete healing will take place eventually even though little or no improvement may occur after the initial period of great encouragement (2) During the period of observation there is the ever present danger that there will be a sudden serious extension of the lesions (3) The loss of time to the patient while waiting during an indefinite period of weeks or months for a complete recovery that unaided sanatorium treatment alone may be unable to produce is not of major importance but may seem so to the patient who in discouragement may abandon medical care

No inflexible rule as to the best time to begin collapse therapy can be given that could be applied properly to all patients Since active pulmonary tuberculosis is a grave disease and potentially so even in its minimal stage the safety of the patient is in my opinion increased greatly if he is given from the beginning whatever forms of treatment are most likely to produce the most rapid healing of his lesions Active pulmonary tuberculosis may be compared with a fire which should be extinguished as quickly as possible by whatever means are necessary and not doused with only a single bucketful of water unless this is reasonably certain to be enough

The early expert use of such a relatively minor and easily borne operation as temporary phrenic paralysis or pneumothorax in minimal or moderately advanced tuberculosis definitely increases the chance of recovery and therefore the patient s safety When however an untreated patient is seen first in the far advanced stage of tuberculosis usually it would be unwise to proceed at once with a thoracoplasty or other major operation even if this operation should be clearly indicated on pathologico-anatomical grounds assuming that a preliminary trial of some less extensive operation were considered useless Instead the patient should be given one or more months of unaided sanatorium treatment in order to improve his general condition in preparation for the strain the thoracoplasty will put upon him A preliminary period of unaided sanatorium treatment is indicated also in some patients who when first seen have bilateral lesions that are of approximately equal gravity since the collapse therapy of such bilateral lesions requires most careful planning knowledge of a tendency of the lesions of one side to improve from bed rest alone might be of great value to the internist and surgeon in helping them to choose the most suitable bilateral operations

A fundamental rule in the surgical treatment of pulmonary tuberculosis is that the least extensive operative procedure that offers a reasonably good chance

of bringing about healing should be used first Also that if suitable for the particular patient a so-called reversible operation e g temporary phrenic paralysis or pneumothorax be used in preference to one that would permanently exclude a part of a lung from function e g thoracoplasty If the first operation used should fail to bring about complete healing the next least extensive operation that offers a reasonable chance of bringing about healing should be used next This plan of procedure is in a sense contradictory to the advice already given namely that whatever treatment is likely to bring about the most rapid healing should be used promptly The problem chiefly concerns the type of case in which there is a tuberculous cavity that is not too large to be closed by phrenic paralysis or pneumothorax but in which closure by these means would be uncertain whereas closure by thoracoplasty would be virtually certain Some physicians feel that thoracoplasty should be used initially in these cases believing that valuable time thereby is saved and that the end results are best I share the opinion of those who believe that a patient fares better if his tuberculosis becomes solidly healed by the minor operation of phrenic paralysis or pneumothorax than if the major operation of thoracoplasty with its resulting considerable permanent impairment of respiratory functional reserve were used to produce healing This statement should however be qualified in two important particulars (1) Neither phrenic paralysis nor pneumothorax should be used unless there is a reasonable chance that the cavity will become completely closed ( ) If phrenic paralysis or pneumothorax with or without intrapleural pneumonolysis is used and does not soon show promise of being completely effective thoracoplasty or another suitable major operation should be accepted without unnecessary delay

The following are the important general contraindications to the use of surgery (1) Hopelessly poor general condition of the patient including tuberculous or nontuberculous extrapulmonary lesions that are in themselves grave (2) Too little cardiorespiratory functional reserve (3) Almost certainly fatal tuberculosis (4) Certain types of complicating tuberculous tracheobronchitis which will be discussed later in this chapter

Choice of Operation

The general indications for surgery have been considered in the preceding paragraphs of this chapter It is virtually impossible to present within the space of a single chapter the specific indications for each operation in view of the large number of variable factors relating to (1) the patient himself his general condition cardiorespiratory functional reserve age physical condition and the amount of fatiguing work he had been doing during the several months preceding the first manifestation of tuberculosis his economic and family status the treatment

he may have had to date, etc , (2) the kind and severity of the signs and symptoms at the time surgical treatment is being considered, fever, night sweats, fatigue, hemoptysis weight, status of digestion, amount of cough and sputum the presence or absence of tubercle bacilli in the sputum or fasting gastric contents dyspnea wheezing extrapulmonary complications etc , (3) the type and extent of the pulmonary lesions as revealed roentgenographically and, if a series of x rays is available the favorable or unfavorable changes that have taken place in the lesions All the factors mentioned in this paragraph must be weighed carefully with regard to the choice of the most suitable operation for the particular patient

The type of the pulmonary lesions obviously is of great importance Extensive fresh exudative lesions which can disappear by absorption or gradually be partly replaced by fibrous tissue should often be handled primarily by temporary phrenic paralysis which rests and relaxes them but usually not by pneumothorax, which too often results in a tuberculous empyema in this particular type of case With regard to lesions that are predominantly fibrotic or productive a distinction should be made in so far as possible between those that are relatively young and therefore capable of contraction, and those that are old and that have expended most of their ability to contract The former tend to contract and close contained cavities with the help of those operations that produce only moderate pulmonary relaxation or collapse whereas the latter often need maximally collapsing operations in order to compress the tough fibrous tissue and close completely cavities within such lesions

The size number and distribution of pulmonary cavities are of prime importance in the choice of the most suitable operation for a particular patient Small or even medium sized up to approximately 6 cm in diameter cavities may become closed by phrenic paralysis provided that the pericavernous lesions are not composed of dense old, fibrous tissue If phrenic paralysis should fail the addition or substitution of pneumothorax may be the wisest next step Circumstances may indicate that pneumothorax is the best primary operation for medium sized or large cavities Pneumothorax may be worth trying for large or even for giant cavities but if indivisible pleural adhesions prevent complete cavity closure after a reasonable trial the pneumothorax should be abandoned and thoracoplasty or other suitable operation used Certain old large or giant cavities that are almost surely bound to the thoracic wall by extensive pleural adhesions should not be treated primarily by pneumothorax but by thoracoplasty or possibly by lobectomy

Bilateral Tuberculosis

Although unilateral pulmonary tuberculous lesions are encountered frequently bilateral lesions occur more often In a great majority of the cases of bilateral

tuberculosis the lesions are more extensive on one side than the other When the lesions of the less extensively diseased lung are not too advanced they often become solidly healed as a result of the patient s improved resistance to tuberculosis that occurs with the healing of the lesions of the more extensively diseased lung following surgical treatment

There are however many patients who have such extensive bilateral lesions that recovery can take place only if surgery can be used bilaterally The decision as to whether surgery can be used bilaterally usually must be based upon whether the patient has sufficient cardiorespiratory functional reserve to permit the bilateral operations his particular lesions require Since extensive bilateral tuberculosis greatly reduces this reserve and perhaps causes mild dyspnea even before any operation has been performed many patients are automatically excluded from the benefits of surgery If it is apparent that bilateral surgery must be used for recovery a fatal outcome obviously cannot be averted if surgery is used only on one side should the cardiorespiratory functional reserve permit this

The determination as to whether a patient has sufficient cardiorespiratory reserve for the contemplated operations or operation in case only unilateral surgery is needed is often the most difficult problem the internist and surgeon must face in the surgical treatment of pulmonary tuberculosis If a patient is even mildly dyspneic after a type of slight exertion in or out of bed to which he is accustomed he can scarcely be expected to tolerate any operation that would exclude an important amount of respiratory function As there is no known measure by which the available functional reserve can be weighed against the operative impairment of the reserve only clinical experience can be used to determine whether a particular patient can safely have a contemplated operation or bilateral operations A number of tests of cardiorespiratory functional capacity are in use and are of value in helping the clinician to make a sound decision Particularly helpful in certain cases is differential spirometry by which various factors concerned in pulmonary function are determined for each lung separately by means of a special bronchoscopic instrument Differential spirometry is especially useful in those cases in which a unilateral thoracoplasty or other major operation is desirable and in which healed or healing tuberculous or nontuberculous lesions e g fibrosis emphysema or extensive pleural adhesions in the other lung apparently have contributed to a considerable total reduction in respiratory reserve If the spirometry tests should show that the function of the lung opposite to that for which the thoracoplasty is needed is greatly impaired the thoracoplasty could not be performed safely

For those patients who seem to have enough cardiorespiratory reserve for bilateral operations a reversible type of operation e g temporary phrenic paralysis or pneumothorax should if suitable be chosen for one or both lungs so as to conserve as much pulmonary function as possible The choice of the

he may have had to date, etc , (2) the kind and severity of the signs and symptoms at the time surgical treatment is being considered fever, night sweats, fatigue, hemoptysis weight status of digestion, amount of cough and sputum the presence or absence of tubercle bacilli in the sputum or fasting gastric contents dyspnea wheezing extrapulmonary complications, etc , (3) the type and extent of the pulmonary lesions as revealed roentgenographically and, if a series of x rays is available the favorable or unfavorable changes that have taken place in the lesions All the factors mentioned in this paragraph must be weighed carefully with regard to the choice of the most suitable operation for the particular patient

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parenchymal tuberculosis should have tuberculous tracheobronchitis and why others should not At the time of the recognizable onset of the complication the patient s general condition may be excellent and the character and extent of the parenchymal lesions as varied as they are in patients who do not have tuberculous tracheobronchitis In fact tracheobronchial lesions may occur when the parenchymal lesions are minimal and without cavitation and exceptionally before there is any evidence of a parenchymal lesion

The thought inevitably comes to mind that tuberculosis of the bronchi is closely related to that of the larynx but apparently this is not true Although these lesions do coexist in some cases and although either one frequently arises in the presence of advanced pulmonary parenchymal tuberculosis laryngeal tuberculosis if not too far advanced like intestinal tuberculosis almost always becomes healed after the parenchymal lesions have been controlled whereas tuberculosis of the trachea and bronchi frequently does not improve after the parenchymal lesions have been controlled In fact an increasing number of cases is accumulating in which ulcerative bronchial lesions have progressed in the bronchial stump and into the trachea after the parenchymal lesions have been removed by pneumonectomy

The lesions of tuberculous tracheobronchitis tend to produce progressive stenosis This statement is obvious for the hyperplastic and fibrotic types of lesion ulcers if they do not soon heal stimulate the formation of fibrous tissue which contracts and thereby produces stenosis When the degree of stenosis has become sufficient atelectasis occurs in that part of the lung supplied by the affected bronchus When the degree of stenosis is not quite sufficient to produce atelectasis collapse of the lung by pneumothorax phrenic paralysis or other operation usually precipitates atelectasis probably because of a narrowing of the bronchi as a result of the relaxation of the lung

Theoretically atelectasis per se is chiefly harmful in excluding pulmonary tissue from function When however the atelectatic portion of the lung is suppurating or contains a cavity interference with bronchial drainage usually creates the same sort of harmful symptoms extension of the parenchymal lesions blocked or tension cavity and development of bronchiectases that occur when a bronchial block is produced in a nontuberculous patient by a carcinoma or a foreign body Only occasionally does a bronchial block that produces atelectasis result in the complete and permanent closure of a tuberculous cavity For these reasons collapse therapy should not as a general rule be used in the presence of unstable bronchial lesions When the bronchial lesions have become relatively stable and when ulceration if present is not progressive collapse therapy may be used Thus thoracoplasty may properly be used when an open cavity exists in an atelectatic lobe or lung and when the stenosing bronchial lesion that produced the atelectasis is fibrotic and contains no ulcer that is progressive

best operation for each lung should be made tentatively before the first operation is performed If a thoracoplasty should be needed for the more extensively diseased lung and if intrapleural pneumothorax or extrapleural pneumothorax or extrapleural pneumonolysis with paraffin filling should be the only suitable operation for the less extensively diseased lung, this operation should be performed first The reason for this is that, if indivisible interpleural and extrapleural adhesions should be encountered thereby preventing closure of the pulmonary cavity the patient would be spared from having the greater operation of thoracoplasty for the opposite lung, if thoracoplasty had been performed first closing the cavity the patient would be little benefited because an open cavity would remain in the other lung The principle of using the lesser operation first in order to determine whether or not it will be effective should not, however, be accepted as a general rule for every case Incidentally bilateral thoracoplasty is used rarely because if the lesions are extensive the necessary thoracoplastic collapse would too greatly impair pulmonary function and if the lesions are not too extensive other operations which impair pulmonary function less are available, at least for one of the two affected lungs

TUBERCULOUS TRACHEOBRONCHITIS*

Approximately 11 per cent of sanatorium patients having the adult or reinfection type of pulmonary (parenchymal) tuberculosis have complicating tuberculous lesions of the bronchi that are of clinical significance In many cases these lesions cause the parenchymal lesions to behave in atypical and unfavorable ways and seriously affect the outlook for recovery

Occasionally the lesions are in the trachea but usually they are confined to the bronchi of one or both lungs In a considerable majority of the cases the lesions are in the larger bronchi and therefore can be seen and treated by means of a bronchoscope but in some cases the lesions of clinical significance are only in the smaller bronchi their presence there being assumed because of rather characteristic symptoms signs and roentgenographic findings Pathologically the lesions may involve all the layers of the bronchi but clinically they are classified according to the appearance of the mucosa as seen bronchoscopically The principal types of lesions are hyperplastic ulcerative and fibrostenotic. As one type probably becomes transformed into another in the sequence given mixed types are seen frequently the ulcerostenotic being the commonest The pure hyperplastic type is relatively rare

No adequate explanation has yet been made as to why some patients with

* The term tuberculous tracheobronchitis should be distinguished from the term tracheobronchial tuberculosis which is tuberculous disease of the peritracheal and peribronchial lymph nodes which only occasionally involves the tracheal and bronchial walls.

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However the use of pneumothorax under similar circumstances usually is not advisable because if adhesions do not prevent a good collapse, atelectasis occurs (if not already present) without complete healing of the tuberculous lesions also the atelectatic lung can only rarely be made to expand fully after abandonment of the pneumothorax

Although the presence of tuberculous tracheobronchitis frequently can be diagnosed from the peculiar symptoms and the roentgenographic behavior of the parenchymal lesions confirmation of the diagnosis and information about the type position and extent of the tracheobronchial lesions can be had only from bronchoscopy Bronchoscopy must be used also for the cauterization of ulcers for the dilatation of certain strictures and for information about the favorable or unfavorable progress of all types of tuberculous tracheobronchial lesions

The old feeling that bronchoscopy would be harmful to tuberculous patients has been dispelled by extensive experience with it during the last twelve years Harmful effects occur only rarely provided that the accepted contraindications to its use are observed and that ulcers and stenoses are not treated too actively and provided of course that the bronchoscopy is carried out expertly

COLLAPSE THERAPY PROCEDURES

Phrenic Nerve Paralysis

Complete paralysis of one phrenic nerve produces complete paralysis of the corresponding hemidiaphragm Since the diaphragm is an important muscle in effecting the inspiratory movement of the lung paralysis of this muscle causes considerable rest of the lung which is a valuable aid to the healing processes of tuberculous lesions and to the stopping of persistent hemoptysis Furthermore paralysis of this muscle causes it to remain in the elevated or expiratory position and with atrophy the diaphragm usually becomes elevated above the normal expiratory position The elevated position has a relaxing or collapsing effect upon the pulmonary lesions which favors the contraction of fibrous tissue in the lesions and therefore the closure of cavities These effects of phrenic paralysis occur in any part of the lung in which there are lesions capable of contraction both physical experiments and clinical experience have shown that apical lesions respond as favorably as do basal lesions

Since the pulmonary rest and relaxation produced by phrenic paralysis are incomplete as compared for example with those produced by thoracoplasty, phrenic paralysis should not be expected to produce complete healing of extensive lesions containing old fibrous tissue that no longer retains the ability to contract Phrenic paralysis however frequently brings about the healing of infiltrative lesions that are not very extensive and not too old, and the closure of cavities

that are less than 3 cm in diameter In some cases phrenic paralysis may prove to be effective for lesions that ordinarily would be considered beyond the healing capacity of the procedure and almost needless to say it may fail in cases in which a good result had been expected

If phrenic paralysis were made permanent and should fail to bring about a satisfactory result the patient obviously would have suffered a permanent injury to his respiratory reserve that might prevent the use of some supplemental curative collapse therapy operation For this reason it is now considered unwise to produce permanent phrenic paralysis at the initial operation except in the rarest circumstances throughout this chapter phrenic paralysis is intended to mean temporary phrenic paralysis Fortunately temporary paralysis for an average period of six months can be produced by the mere crushing of the main phrenic nerve and the crushing or resection of all small accessory phrenic nerve roots in the lower posterior cervical triangle

If a six months period of phrenic paralysis should not have a satisfactory effect upon the lesions the patient would have regained the respiratory capacity he had prior to the phrenic paralysis Then or before if a few months trial of paralysis should fail to give a reasonable promise of success and if the respiratory capacity were sufficient some other collapse therapy operation that is considered suitable for the particular patient would be used

If however a six months period of phrenic paralysis closes a pulmonary cavity and has a favorable effect upon the infiltrative lesions it is of great importance that a second and probably a third six months period of paralysis be produced by additional operations Each successive period of paralysis should be produced as soon as fluoroscopy shows beginning return of diaphragmatic movement even though paradoxical movement persists with the sniffing test so as to prevent a reopening of the cavity and a reactivation of the infiltrative lesions Many patients have lost their chance to recover completely from tuberculosis because a second or a second and a third period of paralysis was not produced after a clinically satisfactory initial period of paralysis The reason for this is that a six months period of pulmonary rest and relaxation whether produced by phrenic paralysis pneumothorax or other procedure only rarely is sufficient to produce solid permanent healing of the lesion

The clinical results of phrenic paralysis are excellent when the operation is used for suitable cases and when it is properly carried out In a considerable number of tuberculosis centers however phrenic paralysis is believed to be an ineffective operation Visits to some of these centers have convinced me that the chief reasons for this belief are (1) The operation frequently has been used for unsuitable cases (2) The operation often has been performed improperly in that (a) the surgeons have been unable to produce complete paralysis for a six month period because of failure to find all the accessory phrenic nerve roots or

(b) they have produced permanent paralysis because of improper treatment of the nerves or (c) severe hemorrhage or paralysis of a part of the brachial plexus, the vagus sympathetic or recurrent laryngeal nerve has resulted because of inexpert surgical technic or ignorance of the variations in the anatomy of the base of the neck (3) Failure promptly to produce second, or second and third six months periods of phrenic paralysis, when the first periods of paralysis had a satisfactory effect

Pneumoperitoneum

The introduction of filtered air into the peritoneal cavity, followed by periodic replacement of the air that is gradually absorbed results in a partial respiratory fixation and elevation of both halves of the diaphragm, since the air rises to the subphrenic space even when the patient lies in bed usually on a spring bed with one or two pillows The partial diaphragmatic rest and elevation produced by pneumoperitoneum cannot be expected to be a powerful aid in the healing of tuberculous pulmonary lesions but it may be sufficient to tip the balance in favor of healing in certain cases Pneumoperitoneum sometimes is used for extensive bilateral lesions for which pneumothorax is impossible because of extensive pleural adhesions and for which a trial of phrenic paralysis would be unwise because of the danger of serious dyspnea and anoxia In such cases complete healing should not be expected, if partial healing occurs, more effective collapsing operations then may be possible

When pneumoperitoneum is used in conjunction with unilateral phrenic paralysis a much greater elevation of the paralyzed half of the diaphragm usually occurs than with phrenic paralysis alone The greater elevation of the hemi diaphragm then may be a determining factor in the attainment of complete cavity closure A somewhat comparable increase in the elevation of a paralyzed diaphragm can be produced by the constant wearing of a Burgess Gordon abdominal belt or diaphragm lift, which has the advantages over pneumoperitoneum of not requiring repeated refills of air and of not exposing the patient to even the small risks of pneumoperitoneum

Pneumothorax

The introduction of small, measured amounts of filtered air into the pleural cavity under manometric control causes collapse and partial rest of the lung which are of great value in closing pulmonary cavities and in aiding in the healing of infiltrative lesions In order to maintain the favorable effects of pneumothorax it should be continued by refills of air at intervals of approximately from one to three weeks during a period of from one to three or more years according to the type response and character of the lesions The greatest advantages of an effec

tive pneumothorax are that it does not require a surgical operation and that upon the termination of treatment the air in the pleural cavity becomes absorbed with resulting expansion of the lung and resumption of pulmonary function

There are however certain disadvantages of pneumothorax therapy (1) Complete obliteration of the pleural cavity by adhesions may prevent the induction of any pneumothorax (2) Adhesions over that part of the lung containing the lesions requiring collapse may prevent an adequate collapse unless the adhesions can be divided by the operation of intrapleural pneumonolysis (3) The development of a clear pleural effusion may result in an obliterative pleuritis with gradual loss of the pneumothorax before it has healed the pulmonary lesions The thickening of the visceral and parietal pleuras and strong adhesion between them resulting from the effusion produce varying degrees of permanent impairment of pulmonary function especially of the lower half of the lung which may not have been affected by tuberculous lesions If the effusion becomes absorbed before obliterative pleuritis occurs the pneumothorax can be maintained but thickening and stiffening of the visceral pleura may have taken place to such an extent that the lung will never expand fully and function adequately after pneumothorax refills have been stopped failure of the lung to expand after abandonment of an old pneumothorax occasionally occurs even though no effusion had been present (4) A pure tuberculous or mixed tuberculous and pyogenic empyema may complicate a simple pneumothorax or may develop from a clear effusion Such an empyema may or may not be accompanied by a bronchopleural fistula An empyema usually results in a greater degree of functional respiratory impairment than does a serous effusion and the lung is less likely ever to expand completely (5) Some patients whose symptoms of active tuberculosis may have disappeared soon after a satisfactory pneumothorax had been induced rebel against prolonged future pneumothorax refills believing that they are no longer necessary and fail to report for refills Under these circumstances the lesions often become reactivated and by the time the patient again seeks medical advice the lung may have expanded completely and probably has become adherent to the parietal pleura thereby preventing reinduction of an effective pneumothorax However a patient who accepts a prolonged period of pneumothorax refills after discharge from a sanatorium receives the incidental important benefit of being under the prolonged supervision of his physician

In spite of its great value pneumothorax is at present relatively unpopular and is being severely criticized in many parts of this and other countries The chief reason for this unpopularity is I believe that far too often a pneumothorax that does not produce adequate collapse of the lesions is maintained indefinitely not only because of some symptomatic improvement and a decrease in the size of a cavity but also because of a mere hope that an inadequate pulmonary collapse eventually will become adequate The complications of pneumothorax that were

described in the last paragraph are much more likely to arise in a patient having an inadequate than an adequate pneumothorax A pneumothorax should be abandoned as soon as it becomes reasonably evident that it is unlikely to bring about complete cavity closure although division of pleural adhesions by the operation of intrapleural pneumonolysis or a supplementary phrenic paralysis operation should be considered and used in suitable cases before a final decision to abandon the pneumothorax has been reached If pneumothorax were used under the limitations described in this paragraph and if it were not used for the pneumonic type of tuberculous lesion it would regain its proper place of usefulness in the collapse therapy of tuberculosis

In a word pneumothorax should be chosen for those lesions which, on the one hand are unlikely to become healed as a result of phrenic paralysis and which on the other hand are not so extensive as almost certainly to require a thoracoplasty for permanent cavity closure

It is virtually impossible to define in writing without reference to specific cases, because of the many factors involved which lesions are best suited to pneumothorax and which to phrenic paralysis In general pneumothorax should be used for cavities having a greater diameter than 3 cm and also for somewhat smaller cavities situated in the extreme apex or close to the visceral pleura Phrenic paralysis should be used for unilateral lesions that are less extensive than those just described, provided that the cavernous and noncavernous lesions are not old and fibrotic Phrenic paralysis should be used initially in preference to pneumothorax for the acute and subacute pneumonic type of tuberculous lesion and also for persisting hemoptysis in cases in which the character of the lesions does not make pneumothorax the preferable procedure

In many clinics phrenic paralysis is never used initially for even a small cavity My strong preference for initial phrenic paralysis in the types of cases just described is based upon its frequent complete effectiveness and upon the avoidance of pneumothorax complications

A combination of pneumothorax and phrenic paralysis often is effective in cases in which a pneumothorax or phrenic paralysis alone has not proved effective With certain exceptions a phrenic paralysis should be added in a case in which a pneumothorax already exists only when the upper and lower parts of the lung are adherent and when the upper adhesions cannot be safely severed by the operation of intrapleural pneumonolysis When phrenic paralysis has been used initially and has failed to produce a satisfactory result the phrenic paralysis will supplement favorably a subsequently produced pneumothorax only if adhesions happen to exist at the upper and lower parts of the lung In occasional cases however the combination of phrenic paralysis and pneumothorax may be of value when the only pleural adhesions are between the base of the lung and the diaphragm

Incidentally phrenic paralysis often is used at the time when a successful pneumothorax is being abandoned in order to diminish the capacity of the hemithorax which the partially shrunken lung must fill and also to diminish the inspiratory tug upon the fibrosed pulmonary lesions during the somewhat critical period of pulmonary expansion

Intrapleural Pneumonolysis

In the section dealing with pneumothorax mention has been made of the frequency with which pleural adhesions prevent adequate collapse of the pulmonary lesions particularly of cavities Such adhesions often have no length since they hold the visceral and parietal pleuras in direct contact with one another when this is so the adhesions cannot be safely severed When however pleural adhesions in a pneumothorax space have length it is possible to divide them by means of a galvanocautery or by diathermic coagulating and cutting currents The dividing element is passed into the pneumothorax space through a cannula which is introduced by means of a trocar through an intercostal space under local anesthesia Manipulation of the dividing element is controlled by sight through a thoracoscope which is similar to a small cystoscope and which is passed into the pneumothorax space through a separate cannula or together with the dividing element through a single cannula

Stereoscopic x rays which ometimes must be made in several projections and fluoroscopy indicate whether the adhesions can probably be divided Actual inspection of the adhesions through the thoracoscope often shows however that they are more numerous and shorter than the x rays indicated On the contrary actual in pection of the adhesions sometimes shows that they may be divided safely in cases in which roentgenology indicates that division would be hazardous or impossible In the division of adhesions the surgeon s chief concern is *to avoid injury of the lung the great vessels and organs of the mediastinum* and the vessels of the thoracic wall Obviously an adhesion that is as short as one half centimeter may be divided with greater safety if it is attached to the costal periosteum than if attached to the vena cava or subclavian artery The width and fibrous density of an adhesion are also of great importance with regard to the possib lity of its safe division Frequently adhesions are found to consist of an intricate maze of free strings or cords and continuous sheets or shelves Sheets and shelves may be triangular in shape having a long free side and an apex where the lung and thoracic wall or mediastinum are held in direct contact with one another In some cases the division of the strings cords and long parts of the sheets or shelves will produce a useful increase of pulmonary collapse but the adhesions that can not be safely divided too often prevent a satisfactory collapse Under certain circumstances it is possible to free the parietal attach

ment of a not too broad mass of adhesions having little or no length from the intercostal muscles and costal periosteum by a dissection with the cautery external to the parietal pleura after a cautery incision of the parietal pleura around the attachment of the adhesion

Adhesions that hold tuberculous lesions under tension tend not only to prevent complete cavity closure but also to delay or prevent solid healing of the non cavernous lesions Generally speaking, such adhesions should be severed, when this can be done safely, as soon as it becomes apparent that further pneumothorax refills will not lengthen the adhesions or cause them to rupture The degree of risk of injury to the lung or mediastinal or thoracic wall structures the surgeon is willing to accept in dividing extensive or short adhesions should be based upon the relationship between their successful division and the patient s recovery A greater than average risk obviously would be accepted for a patient with bilateral cavernous tuberculosis for whom closure of the cavity on the side of the only possible pneumothorax might be a necessary preliminary to the use of some collapse therapy procedure for the other lung However, in the case of a patient with unilateral tuberculosis having such extensive or short pneumothorax adhesions that intrapleural pneumonolysis would be risky, this operation should not be used instead phrenic paralysis should be added to the pneumothorax, if this combination were suitable for the particular case or the pneumothorax should be abandoned and a thoracoplasty performed

In occasional cases the necessity for the division of the offending adhesions is so great that they should be divided by the operation of open intrapleural pneu monolysis if the closed operation is not feasible Improvements in operative technic now permit the division of extensive short adhesions through a wide thoracotomy incision without great risk

Oleothorax

The substitution of mineral olive or other oil for the air of a pneumothorax creates an oleothorax The chief usefulness of oleothorax is in those cases of pneumothorax in which an obliterative pleuritis that is causing a premature expansion of the lung can be effectually combated in no other way oleothorax however does not consistently accomplish this objective Oleothorax which requires infrequent refills also is used occasionally to maintain the pulmonary collapse produced by a pneumothorax which is so small or so localized that the necessarily frequent refills of air needed to maintain the pneumothorax would be very difficult to make In some cases oleothorax proves effective in checking persistent pleural effusion and even in controlling tuberculous empyema

An established oleothorax space may maintain itself indefinitely without refills or with refills at intervals of months A feared complication of oleothorax

however is that a pleural effusion or a progressive obliterative pleuritis will so greatly increase the intrapleural pressure that a bronchopleural fistula will develop with consequent expectoration of the oil and infection of the pleural cavity and possibly an aspiration pneumonia

Extrapleural Pneumothorax

When pleural adhesions are so extensive in a pneumothorax that neither closed nor open intrapleural pneumonolysis could be used effectively to collapse the affected portion of the lung or when no pneumothorax at all can be produced the lung together with the adherent visceral and parietal pleuras can be separated surgically from the thoracic wall and air introduced into the extrapleural space that has been created Although the lining of this space is composed of connective tissue without covering serosal cells it retains the air Such an extrapleural pneumothorax must be maintained by refills of air as in an intrapleural pneumothorax A relatively high pressure must be used in the extrapleural space in order to prevent obliteration of the space by adhesions

Theoretically extrapleural pneumothorax is in many ways an ideal procedure since (1) it can be created selectively over that part of the lung needing collapse leaving the uncollapsed normal portion of the lung for pulmonary function (2) it can be used for the many patients who are prevented from having an adequate pulmonary collapse by interpleural pneumothorax because of interpleural adhesions and (3) after collapse is no longer needed abandonment of the refill of air should but actually frequently fails to result in expansion of the collapsed portion of the lung and a return of it temporarily restricted function Five or six years ago these advantages caused many clinics to adopt extrapleural pneumothorax with great enthusiasm and to use it in many cases in preference to thoracoplasty even when there was no contraindication to thoracoplasty At present many of these clinics do not use the procedure at all and others use it only occasionally

The reasons for the operation s loss of popularity are that (1) the surgical opening of the extrapleural tissues which often contain tuberculous lymphatic vessels too often results in a tuberculous extrapleural empyema which may lead to a breaking down of the operative incision in the thoracic wall or to perforation into a bronchus (2) tough extrapleural adhesions may result in the surgeon s tearing the diseased lung which has grave consequences or in his failing to divide these adhesions and produce an adequate pulmonary collapse (3) postoperative hemorrhage may take place in the extrapleural space (4) obliteration of the extrapleural space may occur in spite of all efforts to prevent it including the use of extrapleural oleothorax and (5) the formation of a dense layer

of scar tissue on the pulmonary wall of the extrapleural space may prevent ultimate expansion of the lung after collapse is no longer needed, in such cases a thoracoplasty is necessary for the obliteration of the space

In spite of this rather formidable list of possible complications extrapleural pneumothorax is an indispensable operation for a small group of patients whose respiratory functional reserve is too low to permit a thoracoplasty and yet is sufficient for an extrapleural pneumothorax This operation may be the only suitable one for one lung in certain cases of bilateral cavernous tuberculosis in which only a thoracoplasty is suitable for the other lung If unexpected distressing dyspnea should occur the extrapleural air may be aspirated in order to restore adequate pulmonary function

Extrapleural Pneumonolysis with Paraffin Gauze or Other Filling

Extrapleural pneumothorax is technically an extrapleural pneumonolysis with a filling of the extrapleural space with air The space may be filled instead with a special paraffin mixture that becomes solid at body temperature or with gauze rubber dam ffexi tissue or other material The paraffin is intended to remain in place permanently Gauze and most of the other filling materials are removed later and the dead space then is obliterated by a thoracoplasty or allowed to obliterate itself by the slow process of wound healing which causes some re expansion of the collapsed portion of the lung There are therefore, obvious disadvantages to any type of filling which must be removed at some later period of time

Although paraffin as a filling usually is retained permanently it has the disadvantage of being a foreign body that may not be tolerated In from 5 to 10 per cent of paraffin cases a communication sooner or later develops between a bronchus and the paraffin bed then slivers of paraffin are expectorated indefinitely, usually requiring the removal of the paraffin filling followed by either a thoracoplasty or slow healing of the wound

Although both air and paraffin fillings of an extrapleural pneumonolysis space expose the patient to the possibility of various serious complications both are indispensable operations for a small group of patients a majority of whom are saved by one or the other of these operations Neither operation should be used if a thoracoplasty would be suitable since the complications of thoracoplasty are fewer and since the result with regard to cavity closure is better The chief reason for the use of one of the extrapleural pneumonolysis operations particularly with a paraffin filling is that it excludes less lung from function than does a thoracoplasty

A paraffin filling is better than an air filling for lesions that are in the uppermost part of the lung provided that the diameter of the cavity for which the operation usually is performed, does not exceed 3 cm The reason for this limita

tion is that a paraffin filling larger than 300 grams should be used rarely since the larger the foreign body the greater the chance of a foreign body complication An air filling is better than a paraffin filling for larger cavities and for those located below the uppermost part of the lung because a much larger extrapleural space is created for an air filling than for a paraffin filling and because air may be withdrawn readily if the patient should be unduly dyspneic

Scalenotomy Scalenectomy

The division or resection of the three scalene muscles eliminates their elevating action upon the uppermost ribs during inspiration Several years ago it was believed in a number of clinics that this action had an important favorable influence upon the healing of apical tuberculous lesion especially when phrenic paralysis was combined with the scalene operation The contribution of the scalene muscles to quiet inspiration is so slight that the elimination of this action can scarcely be expected to have a healing effect and the clinical results were so disappointing that the procedure now has been virtually abandoned

Intercostal Nerve Paralysis

The crushing of the posterior portions of the intercostal nerves temporarily eliminates the respiratory action of the intercostal muscles and causes the ribs to remain in the expiratory position The lung and its lesions thereby are partially rested and relaxed When in addition to this procedure the phrenic nerve is paralyzed and perhaps the scalene muscles divided or resected the action of quiet inspiration upon one lung is virtually abolished except where the movement of the opposite hemithorax is feebly transmitted to the anterior chest by way of the sternum and the hemithorax assumes the cadaveric position Probably the only useful application of these combined operations is for those patients who have an unusually active toxic type of unilateral tuberculosis for which bed rest and phrenic paralysis alone have proved insufficient and for which pneumothorax may not be advisable because of the danger of pleural complications Under such conditions the combination of intercostal nerve paralysis phrenic paralysis and perhaps division or resection of the scalene muscles has not rarely proved life saving The indications however are few and the combination of operations should not be used for dyspneic patients or those having abundant sputum The relaxation of the lung is not sufficient to close any but small cavities if a large cavity is present therefore pneumothorax thoracoplasty or other suitable operation will need to be used at such time as the improvement in the patient s condition permits

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so often contains the cavity If there is any doubt about a cavity in the upper lung having become completely closed after the removal of the posterolateral portion of the uppermost seven or eight ribs an anterior thoracoplasty stage should be performed at this operation the anterior stumps of the uppermost three or four ribs and the first costal cartilage should be removed and the other cartilages divided at their junction with the sternum or these cartilages may be removed and their perichondrial sheaths filled with costal osteoperiosteal bone grafts in order to stabilize the anterior thoracic wall

As a further aid to maximal collapse of the upper lung Semb proposed that at the first stage of a thoracoplasty the upper part of the lung be freed from its fascial attachments so that it would descend and collapse farther in a vertical direction than it does in a thoracoplasty without this *Semb apicolysis* This procedure tends to prevent a cavity from remaining open as a vertical slit against the mediastinum Apicolysis should in my opinion be used only for relatively large cavities in the extreme apex of the lung or for those whose mesial wall lies close to the mediastinum before thoracoplasty because such cavities are the ones that most often remain open as a vertical slit after a simple thoracoplasty Cavities located below the extreme apex probably are not helped to close by a Semb apicolysis since they are depressed in the hemithorax to a position where the chest is wide in both its anteroposterior and horizontal directions and where therefore thoracoplastic collapse is less efficient than in the uppermost chest Another reason why apicolysis should not be used routinely is that dissection in the extrapleural plane opens lymphatic channels that may be tuberculous thereby exposing the patient to the danger of tuberculous infection of the wound

When a patient has a residual cavity after the completion of a thoracoplasty a revision or secondary thoracoplasty should be performed if at the primary thoracoplasty insufficient lengths of ribs or transverse processes were removed provided that the improved pulmonary collapse expected from the secondary thoracoplasty would probably close the residual cavity When however the primary thoracoplasty produced virtually maximal collapse a secondary thoracoplasty would prove futile In such cases surgical drainage of the cavity or lobectomy should be considered provided that bronchoscopy reveals no contraindication

It is not within the scope of this chapter to consider those many details of operative technic and of preoperative preparation and postoperative care of the patient that are of vital importance for the production of excellent clinical results including good function of the shoulder girdle and the avoidance of scoliosis The great majority of patients for whom thoracoplasty has been carried out properly recover completely from their tuberculosis have so little change in the external configuration of their chest that when clothed the side upon which the operation was performed cannot be detected have virtually normal move

Extrapleural Thoracoplasty

Thoracoplasty is the collapse therapy procedure that is used in suitable cases when those less extensive procedures that might have been effective for a particular patient have been tried and have failed Thoracoplasty is used also as a primary collapse therapy procedure for patients having far advanced tuberculosis and such large cavities that only a thoracoplasty could reasonably be expected to close them

A thoracoplasty produces permanent collapse of that part of the lung over which the ribs are removed In the earliest thoracoplasties only short sections of a few ribs were removed but the resulting pulmonary collapse rarely was sufficient to close the pulmonary cavities Gradually, as the years passed greater lengths of a greater number of ribs were removed with progressive improvement in the percentage of cavities that were completely closed At first the necessary number of ribs were removed at a single operation but the sudden great pulmonary collapse and paradoxical respiratory movement of the decostalized portion of the thoracic wall frequently resulted in death from cardiorespiratory failure At present the necessary number of ribs are removed in operative stages two and a half or three weeks apart When no more than two or two and a half ribs are removed at each stage and when the costal cartilages and anterior portions of the ribs are not removed at the same stage as are the posterolateral portions of the ribs cardiorespiratory failure is rare

The great majority of lesions requiring thoracoplasty are located in the upper third or half of the lung For these lesions only the uppermost seven or eight ribs need to be removed usually in three stages If fewer than seven ribs are removed the inferior part of the scapula is likely to rest upon unresected ribs which prevent the scapula from bedding in and producing maximal pulmonary collapse Furthermore a scapula held out by unresected ribs may cause considerable pain A scapula which has bedded in after the resection of six ribs is held in an elevated position by the unresected seventh rib and in the case of an exceptionally long scapula by both the seventh and eighth ribs If such a patient has a low respiratory functional reserve and if the resection of only six ribs produces adequate collapse of his lesions the inferior portion of the scapula may be resected in preference to resection of the seventh or seventh and eighth ribs

It is apparent that the greatest possible collapse of the cavernous area of the lung will produce the highest percentage of completely closed cavities Since no one can foretell how resistant any cavity even a small one will be to complete closure by thoracoplastic collapse maximal collapse should be sought The removal of the extreme posterior portions of the ribs but not their heads and the entire length of the transverse processes of the vertebrae greatly increases the collapse of that part of the lung which is in the costovertebral gutter and which

only half as great as in their own series of cases There is however general agreement with Vineberg and Kunstler that tension within a cavity probably is the most important cause of the failure of a properly performed thoracoplasty to effect complete cavity closure Only further experience will determine whether or not all cavities should be needled in order to determine their pressures and whether all tension cavities should be Monaldi-drained before thoracoplasty

Until these things have been determined Monaldi drainage should be used preliminary to thoracoplasty for large tension cavities of the type that experience has shown are likely not to become completely closed by thoracoplasty alone In those occasional cases in which the cavity becomes completely closed except for the space occupied by the draining catheter a thoracoplasty should be performed because experience has taught that such closed cavities are likely to reopen after the removal of the catheter unless the lung has been collapsed by thoracoplasty For giant tension cavities an anterior thoracoplasty stage should be performed before anterior Monaldi drainage which should later be followed by the posterolateral thoracoplasty stages

Open Cavity Drainage

Surgical drainage of a tuberculous cavity is carried out in virtually the same way as drainage of a nontuberculous abscess The principal indication is for cavities that have not become closed as a result of a thoracoplasty which has produced maximal pulmonary collapse Such cavities are usually too small and too close to the mediastinum for the safe introduction of a Monaldi tube Occasionally large cavities are drained openly in preference to Monaldi drainage before a thoracoplasty has been performed

Openly drained tuberculous cavities may require dressings for many months before they become completely healed and covered by skin and some of the tuberculous wounds which usually are between the spine and scapula are very tender Cavities that remain open after months of drainage sometimes can be closed with a pedicled muscle or skin graft Open cavity drainage usually is performed only when no other form of treatment offers the patient a chance of recovery the occasional perfect result justifies the disadvantage of the operation in well selected cases

Lobectomy and Pneumonectomy

The fact that no collapse therapy operation gives assurance that the cavity will become closed or the noncavernous lesions completely healed theoretically makes the removal of a tuberculous lobe or lung an attractive form of treatment when the lesions apparently are confined to the part of the lung to be removed How

ments and strength of the shoulder girdle and are able to lead practically normal productive lives

Operations Directly upon the Lung

Monaldi Cavity Drainage

The introduction of a catheter by means of a trocar and cannula into a cavity, followed by constant or intermittent suction upon the catheter is called Monaldi cavity drainage Its chief use is for so-called tension or pressure or balloon cavities in which the air pressure is greater than that of the atmosphere because of a bronchial check valve mechanism which permits air to enter the cavity more freely during inspiration than it can escape during expiration The check valve mechanism usually is produced by an active or fibrosed tuberculous lesion of a large or small bronchus leading from the cavity Monaldi cavity drainage reduces cough and sputum or causes them to disappear if the drained cavity is the only lesion producing sputum In many cases prolonged aspiration of the cavity so cleanses and stimulates its walls that the aspirated discharge becomes scanty and free from tubercle bacilli

When the positive pressure within a tension cavity is reduced by aspiration to an atmospheric or negative pressure the cavity usually becomes smaller and, in some cases, beomes completely closed The fact that the great majority of cavities did not become completely closed and that certain complications occasionally occurred because of the catheter drain led to a rapid cooling of the enthusiasm that was widely expressed during the early months of trial of Monaldi drainage The hope of some clinicians that Monaldi drainage would be a satisfactory substitute for thoracoplasty was abandoned At present usually it is used alone for palliation of distressing cough or in an effort to reduce the size of huge unilateral or bilateral cavities so that a thoracoplasty or other operation may then be carried out with a reasonable hope of success

In a recent article Vineberg and Kunstler state that thoracoplasty alone rarely closes tension cavities, and they recommend Monaldi drainage preliminary to thoracoplasty in all cases in which manometric readings show that the cavity is a tension one They found tension cavities in 27 or 42 9 percent of their series of 63 patients who were to have thoracoplasty the cavities became completely closed in 67 per cent of this group of 27 patients following successive Monaldi drainage and thoracoplasty and in 91 per cent of the 25 patients who did not have tension cavities and for whom thoracoplasty alone was used The fact that approximately 85 per cent of cavities become closed after the modern type of thoracoplasty without preliminary Monaldi drainage seems to prove that Vineberg and Kunstler are wrong in stating that tension cavities rarely close with thoracoplasty alone even if the general incidence of tension cavities were

of the bronchial tump the percentage of patients having undergone lobectomy or pneumonectomy who subsequently are without tubercle bacilli in their sputum or gastric contents is less than was anticipated

The risks of lobectomy are smaller than those of pneumonectomy and obviously the reduction of respiratory functional reserve is less The presence of extensive active lesions in more than one lobe however may require pneumonectomy rather than lobectomy Also a lobar lesion adjacent to an interlobar fissure may extend into adhesions in the fissure or traverse the fissure and invade the neighboring lobe in either event the division of active tuberculous lesions in the fissure in preparation for a lobectomy exposes the patient to the dangers of a postoperative tuberculous empyema In such cases therefore a pneumonectomy usually needs to be carried out instead of the intended lobectomy

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ever from a practical standpoint the operative mortality rate and the percentage of postoperative complications are so much higher than those of any of the collapsing operations that pulmonary resection will never I believe supplant collapse therapy as a routine measure even in unilateral tuberculosis

Because of the relatively high operative mortality and postoperative complication rates lobectomy and pneumonectomy should be used only for those cases in which no other treatment seems likely to succeed These cases include patients who have some of the following features (1) High grade nonulcerative bronchial stenosis with great difficulty of expectoration persisting toxicity from retention of pulmonary secretions and with or without tension cavities and bronchiectases This indication may exist before a thoracoplasty has been undertaken or after an unsuccessful thoracoplasty (2) Large tension cavity in the lower lung providing that surgical cavity drainage is unsuitable in the particular case (3) Extensive caseous lesions with or without a peripheral type of tuberculous bronchitis that have not become healed following prolonged adequate collapse by pneumothorax or thoracoplasty Even these indications are not absolute since many circumstances in individual cases might make resection inadvisable There is a borderline group of cases in which pulmonary resection may exceptionally be preferable to thoracoplasty These cases include (a) certain large tension cavities but without ulcerative tuberculous bronchitis near the intended site of division of the bronchus (b) certain cavities remaining after maximal thoracoplasty collapse although surgical cavity drainage probably is safer (c) large bilateral upper lobe cavities for which no combination of collapse therapy procedures is suitable if pneumothorax has failed to close the cavity in at least one lung (d) a unilobar cavity in a child for which pneumothorax and perhaps, phrenic paralysis have failed thoracoplasty in children tends to produce severe scoliosis and (e) certain densely cirrhotic cavernous tuberculous lesions occupying the greater part of a lobe especially a lower or middle lobe which thoracoplasty probably would be unable to heal

Until the last three or four years lobectomy and pneumonectomy were used only for such restricted indications as are given in the first part of the last paragraph Recently several clinics have extended the indications broadly and have even used resection in preference to thoracoplasty, when the classical indications for thoracoplasty were good In these series of cases the operative mortality has ranged from 6 2 to 28 5 per cent , being 11 4 and 13 6 per cent respectively, in the two largest series The incidence of potentially grave postoperative complications in the patients who were alive at the time the reports were made was high, these complications include spread to or reactivation of tuberculosis in remaining portions of the lung or lungs empyema, bronchopleural fistula tuberculous wound infection and persisting tuberculous infection of the bronchus at the site of its division Because of spreads reactivation and tuberculous infection

CHAPTER XIII

LEPROSY

By LIEUTENANT COLONEL JAMES STEVENS SIMMONS

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of typical lesions containing the lepra bacillus *Mycobacterium lepræ* of Hansen The characteristic pathological lesions occur chiefly in the peripheral nerves and skin producing a great variety of functional circulatory and structural changes which eventually result in extensive mutilations of the face and extremities The disease may last for many years and it usually follows a slow course, interrupted at irregular intervals either by acute reactions or by periods of quiescence or improvement Leprosy of itself does not commonly cause death but because of the unusual susceptibility of lepers to other infections the mortality often is high Many drugs have been used for treatment and reports indicate that the derivatives of chaulmoogra and other related oils are of decided value however no completely satisfactory specific agent is available either for the cure of the disease or for its prevention

History and Distribution

Historical — The origin of leprosy is unknown but it is believed to be a disease of great antiquity There has been much controversy as to the exact nature of the chronic disfiguring skin diseases described in such ancient records as the Bible the Ebers Papyrus the Rig Veda and in early Chinese and Japanese books but it is agreed that they probably included leprosy along with other conditions Gay (1935) commented on this subject as follows According to modern writers (Klingmuller) the pre Christian references to leprosy are necessarily clouded by the doubt of exact identification There seems however no reason to question from this author s review of the evidence that three or four endemic foci of the disease existed before the Christian Era namely in China in India in Babylon and probably also in Egypt The Egyptian focus presupposes moreover a central African origin such as exists at the present time

It seems probable that the disease spread to Europe before the time of Christ and that this resulted largely from the intermingling of peoples incident to extensive military expeditions For example during the fifth century B C Xerxes is said to have led into Europe six million people from all the nations of Asia and Africa under his rule leaving thousands behind when he retired (Rogers and Muir 1925) Aristotle described leprosy about 345 B C and probably it was common in Asia Minor on the Greek coast about 200 B C After the return of Pompey s soldier from the East in 62 B C leprosy became known in Italy and its subsequent spread throughout Europe probably was influenced by the movements of Roman troops and later by the returning Crusaders

During the second and third centuries it was recognized in the Mediterranean countries and in Northern Europe and it increased gradually in other regions By the sixth century leper segregation laws had been passed and asylums had been built During the tenth century leprosy was common in France and was known in Ireland England and Wales in the eleventh century it was reported in Norway and soon thereafter in Denmark and Sweden The disease appears to have reached its highest prevalence in Europe in the thirteenth century and to have decreased markedly during the fourteenth and fifteenth centuries This reduction which was maintained has been ascribed to various factors including (a) the elimination of leprous populations by severe epidemics of bubonic plague and other diseases (b) the development of improved living conditions with better sanitation and hygiene and (c) especially to the strictly enforced laws requiring the segregation of lepers

No such decrease in leprosy has occurred in China India or Africa and from these ancient foci the disease has continued to spread to various other regions It may have been introduced into the Western Hemisphere by Spanish and Portuguese explorers and colonists but a more important factor was the importation of large numbers of slaves from Africa Its introduction into Hawaii New Caledonia the Marquesas the Straits Settlements Borneo the Philippines and Australia has been attributed mainly to migrations of the Chinese

Present Distribution — It is estimated that at present there are between six and seven million lepers in the world (Muir 1937) While the disease occurs in practically every country McCoy (1935) states that the principal foci are in India China Japan Africa and the islands of the Pacific According to Rogers and Muir (1925) the areas of greatest prevalence include parts of the following tropical regions (1) Equatorial Africa which shows the highest rates in the world i e from 5 to 130 per 1000 population (2) an Indo Malay Oceanic area with rates from 1 6 to 33 per 1000 and (3) the West Indies and the north of South America with rates from 1 to 25 per 1000 The disease also is widely distributed in the subtropical zone of 23½ to 35 latitude but rates higher than 1 per 1000 are rare except in a few places including Crete Central China Korea and Southern Japan In temperate regions located in latitudes higher than 40 including Europe the northern parts of Asia and North America and southern South America the rates usually are less than 1 per 1000 however within the last century they have been higher in Iceland Norway and Japan The results of a recent survey (McKinley 1935) of the incidence of leprosy in various countries of the world are shown in Table 1

TABLE I

Summary of Incidence of Leprosy

[McKinley (1935) A Geography of Disease Geo Washington Press Washington p 414]

PLACE	NUMBER OF CASES
United States of America	
15 Selected States	53[1]
Hawaii	5[illegible]
Puerto Rico	80 to 300
Virgin Island	80
Canal Zone (see Panama)	
Guam	8
Philippine Island	25 000
Samoan Islands	0
The British Empire	
Kenya Protectorate	470
Uganda Protectorate	3 081
Tanganyika Territory	838
Nyasaland Protectorate	358
Zanzibar Protectorat	281
Somaliland Protectorate	29
Colony of Nigeria	9 410
Gold Coast Colony	11 216
Colony of Gambia	192
Sierra Leone	244
Basutoland	774
Bechuanaland Protectorate	12
Southern Rhodesia	3 500
Northern Rhodesia	184
Union of South Africa	5 000
The Anglo-Egyptian Sudan	7 500
Mauritius	66
Seychelles	90
Palestine	21
Empirate of Trans-Jordan	R
Cyprus	100
Gibraltar	2
Maltese Islands	11
Sarawak	27
Brunei	2
British North Borneo	74
Ceylon	1 500
India and Dependencies	60 577
Straits Settlements and Federated Malay States	2 804
Burma	2 766
Johore	220
Kedah and Perlis	133
Kelantan	54
Trengganu	45
Hong Kong	1 000
Fiji and Western Pacific	3 000
British Solomon Islands	500
Gilbert and Ellice Islands	32
Commonwealth of Australia	7
Bahamas	20
Barbados	8
Bermuda	11
British Guiana	600
Jamaica	3
Antigua	31
Dominica	32
Montserrat	1
Virgin Island	?)
Grenada	14
St Lucia	25
St Vincent	19
Trinidad and Tobago	9
Republic of France	
Syria and Lebanon	+(?)
Morocco	225
Madagascar	1 068
Reunion	20
West Africa & Sahara	12 020
Equatorial Africa	9 000
French Indo-China	15 000
Pacific Group	868
Guadeloupe	+( )
Martinique	300
Atlantic Group (others)	
Guyane	84
St Pierre	
Miquelon	
Indian Ocean Group	+(?)
The Netherlands	
Dutch East Indies	+( )
Other Countries	
Abyssinia	+( )
Albania	0
Bolivia	+( )
Brazil	6 655
Chile	30
China	1 000 000
Colombia	7 347
Belgian Congo	150 000
Costa Rica	00
Dominican Republic	70
Egypt	10 000
Greece	600
Haiti	40
Holland	100
Honduras	23
Italy	16
Liberia	+( )
Panama and Canal Zone	100
Paraguay	+( )
Peru	0
Spain	+(?)
Siam	405
Turkey	00
Venezuela	46
Yugoslavia	70
Total	1 3 7 094

[1] Does not include some 350 cases isolated at Carville La

[2] According to a recent report by Major General J D Graham it is probable that an estimate of 1 000 000 cases of leprosy in India is not too high

EPIDEMIOLOGY

The present high incidence of leprosy in certain humid tropical regions suggests that its distribution might be influenced by climate. Temperature alone however probably is of minor importance since the disease has been prevalent also in temperate and cold countries. While humidity has been seriously considered as a possible factor, its significance has not been determined. It appears that there is no well defined racial susceptibility or immunity to this disease, which was prevalent in the white race during the Middle Ages and now occurs chiefly among negroes, mongols and malays. More importance is attached to the fact that the disease always has been most prevalent in regions where the standards of living are low and among ignorant primitive people who live in crowded unsanitated dwellings, subsist on inadequate diets and fail to practice even the rudiments of hygiene.

Leprosy attacks individuals of all ages but it is seldom observed in infants. Its incidence is highest during childhood and early adult life and surveys indicate that more than half of the cases probably become infected before the age of twenty years (Rogers and Muir 1925, Wade and Rodriguez 1927). Certain workers (Manalang 1932) even suggest that infections rarely occur in adults and that leprosy is primarily a disease of childhood. In individuals less than five years of age the disease may be more common among females than males but in older age groups the incidence among males often is two or three times as high as among females. Such differences may be due to various unknown factors which influence the degree and manner of exposure.

Transmission. — The method by which leprosy is transmitted still is unknown. During the nineteenth century the observed tendency of the disease to occur in family groups led many to suspect that its origin might be hereditary (Danielssen and Boeck 1848). This theory became widely accepted and remained in vogue until Hansen's discovery of the lepra bacillus revived the ancient belief in contact transmission. Another suggestion no longer seriously considered is the hypothesis advocated by Hutchinson from 1863 to 1900 that leprosy might be caused by the ingestion of improperly preserved or decomposed fish.

(a) *Lower Animals.* — The occurrence of leprosy like diseases in certain lower animals has led to speculation as to whether such animals might afford a reservoir for the etiological agent of human leprosy. This has been especially true in the case of rat leprosy (Stefansky 1903, Rabinowitz 1903, Dean 1903) which resembles the human disease in so many ways that some investigators suggest that the two may be identical (Walker and

TABLE I

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PLACE	NUMBER OF CASES	PLACE	NUMBER OF CASES
United States of America		Antigua	31
15 Selected States	53[1]	Dominica	32
Hawaii	56	Montserrat	1
Puerto Rico	80 to 300	Virgin Islands	(?)
Virgin Island	80	Grenada	14
Canal Zone (see Panama)		St Lucia	25
Guam	8	St Vincent	19
Philippine Island	25 000	Trinidad and Tobago	9
Samoan Island	0		
		Republic of France	
The British Empire		Syria and Lebanon	+(?)
Kenya Protectorate	470	Morocco	225
Uganda Protectorate	3 081	Madagascar	1 068
Tanganyika Territory	858	Reunion	20
Nyasaland Protectorate	358	West Africa & Sahara	12 020
Zanzibar Protectorate	281	Equatorial Africa	9 000
Somaliland Protectorate	29	French Indo-China	15 000
Colony of Nigeria	9 410	Pacific Group	808
Gold Coast Colony	11 216	Guadeloupe	+(?)
Colony of Gambia	19	Martinique	300
Sierra Leone	244	Atlantic Group (others)	
Basutoland	774	Guyane	
Bechuanaland Protectorate	12	St Pierre	284
Southern Rhodesia	3 500	Miquelon	
Northern Rhodesia	184	Indian Ocean Group	+(?)
Union of South Africa	5 000		
The Anglo-Egyptian Sudan	7 500	*The Netherlands*	
Mauritius	66	Dutch East Indies	+( )
Seychelles	90		
Palestine	21	*Other Countries*	
Empirate of Trans-Jordan	R	Abyssinia	+( )
Cyprus	100	Albania	0
Gibraltar	2	Bolivia	+(?)
Maltese Islands	11	Brazil	6 655
Sarawak	27	Chile	30
Brunei	2	China	1 000 000
British North Borneo	74	Colombia	7 347
Ceylon	1 500	Belgian Congo	150 000
India and Dependencies	60 577	Costa Rica	00
Straits Settlements and Federated		Dominican Republic	70
Malay States	2 804	Egypt	10 000
Burma	2 766	Greece	600
Johore	220	Haiti	40
Kedah and Perlis	133	Holland	100
Kelantan	54	Honduras	23
Trengganu	45	Italy	16
Hong Kong	1 000	Liberia	+(?)
Fiji and Western Pacific	3 000	Panama and Canal Zone	100
British Solomon Islands	500	Paraguay	+( )
Gilbert and Ellice Island	32	Peru	0
Commonwealth of Australia	7	Spain	+(?)
Bahamas	20	Siam	405
Barbados	85	Turkey	100
Bermuda	11	Venezuela	46
British Guiana	600	Yugoslavia	70
Jamaica	23	Total	1 357 094

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(e) in many instances the early lesions appear in parts commonly exposed to contact or to insects (f) the incidence has been reported as high as 33 to 64 per cent among children of lepers who remain in contact with their parents (Muir 1930 Manalang 1932) and much lower among such children separated from them at birth (g) infections have been reported in persons following short periods of exposure in endemic areas (Rosenau 1935) and (h) the introduction of the disease into certain nonendemic region has been followed by comparatively rapid spread which can be traced from one individual to another On the other hand the contagiousness of leprosy has been questioned because of (a) failure to obtain a history of contact with a previous case in more than 29 to 89 per cent of patient (b) the infrequency of infections among the doctors nurses and attendants in leper institutions (c) the low incidence of conjugal infections reported by many observers (McCoy and Goodhue 1913) and (d) the failure of many experimental and accidental inoculations of leprous materials to reproduce the disease (Manalang 1932)

The first of these objections might be eliminated on the basis of the difficulty of obtaining accurate histories in a disease characterized by a long incubation period and the others assume less importance if one accepts the evidence indicating that adults are relatively insusceptible to leprosy Considering all the evidence it seems likely that contact is an important means of transmission especially during childhood

Etiology

Mycobacterium lepræ — Leprosy is characterized by the reproduction in the body tissues of *Mycobacterium lepræ* (syn *Bacillus lepræ* Hansen 1874) an organism which was seen first by Hansen in association with the so called globoid bodies of skin lesions and described by him as the causative agent This bacillus is found so consistently in certain typical lesions that its demonstration is now recognized as an important diagnostic aid and although failure to fulfill Koch's postulates has caused some doubt as to its exact etiological significance it is accepted generally either as the cause of leprosy or as a phase in the development of the specific agent

In neural leprosy the bacilli may not be demonstrable in the skin but usually they can be found in the affected nerves In the cutaneous type of the disease they are numerous in the corium of the skin and as the case advances they may be found also in other organs A few reports indicate that the organisms may have been demonstrated in the blood particularly during the febrile attacks in advanced cases

Sweeney 1929 Salle 1934) This opinion is not accepted generally but the possibility deserves further intensive study

(b) *Insects* — Considerable attention has been given to the possibility that insects may act as vectors of leprosy The itch mite *Acaris scabiei* has been suspected because of its common association with lepers (Gomez 1922) Many investigators have reported finding acid fast bacilli on the feet and bodies and in the intestines of flies fed on leprous ulcers also such bacilli have been observed in the intestinal contents of lice ticks bed bugs fleas and mosquitoes subsequent to the feeding of these arthropods on lepers St John Simmons and Reynolds (1930) observed that after *Aedes ægypti* had ingested a saline suspension of *M lepræ* the organisms were demonstrable in the intestines for about five days Vedder (1930) attempted to transmit leprosy to man through the bites of *A ægypti* containing *M lepræ* While visible infection has not occurred during the several years of observation this does not eliminate the possibility of mosquito transmission as negative results are obtained commonly even when leprous materials are inoculated directly into the skin of adults Thus considering all the evidence it appears that the question as to whether insect transmission occurs cannot be answered at this time and that more investigative work should be done

(c) *Soil* — Walker (1929) after finding in soil a species of actinomyces similar in appearance to one isolated from cases of leprosy suggested that the disease might be transmitted through contact with soil contaminated by this organism While the organism has not been shown to be of etiological significance this observation is of interest in connection with the high incidence of infection reported among bare footed individuals of certain regions (Rogers and Muir 1925)

(d) *Contact* — At present it is generally believed that leprosy is transmitted commonly by close and prolonged contact between lepers and young normal individuals That contact was accepted as a method of transmission at an early date is indicated by the energetic measures adopted for the segregation of lepers in various parts of the world Arguments in favor of contact transmission include the following (a) leprosy rates have decreased most in countries in which isolation has been most rigidly enforced and where the standards of living and hygiene have been improved (b) in endemic areas the incidence usually varies in direct proportion to the density of population (c) the disease has a tendency to spread in certain family or household groups (d) infections are more frequent among persons associated with lepers who have open ulcerating skin lesions containing numerous *M lepræ* than among those in contact with patients afflicted with the closed or neural form of the disease

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bacillus appears to be low if one may judge from the slight general reactions produced in certain patients whose tissues contain enormous numbers of organisms. Little is known concerning immunity to leprosy and such immunological tests that have been used fail to indicate the specific nature of *M. lepræ*.

Pathogenesis

The available information concerning the pathogenesis of leprosy is in many respects inadequate. Experimental attempts to reproduce the disease have failed, the method of its natural transmission is unknown, and the etiological relationship of *M. lepræ* to the disease has been questioned.

Predisposing Factors.—The relatively low incidence of leprosy even among contacts and the lack of toxic symptoms observed in patients with numerous *M. lepræ* throughout the body indicate either that the virulence of the infective organism is low or that the resistance of the average individual usually is high. Epidemiological studies show that the disease is contracted more frequently in certain endemic regions by undernourished individuals of unhygienic habits, especially children, after long contact with infected persons, and that often the early lesions occur on exposed parts of the body.

Portal of Invasion.—The causative organism can enter the body by way of the gastrointestinal, genitourinary or respiratory tracts, but the skin and the nasal mucosa have been regarded as the most likely portals, largely on the assumption that the primary lesions usually occur in one of these tissues. As nasal lesions are common, especially in advanced leprosy, the nose previously was considered an important site of infection (Sticker, 1897; Heiser, 1916), but this is questioned now in view of the observations of Gomez and his associates (1922) and others. Solis and Wade (1925) in a survey of 250 children of leprous patients failed to find *M. lepræ* in the nose prior to skin involvement.

The evidence indicating that invasion occurs through the skin is based largely on the observed tendency of early lesions to appear on exposed parts of the body and a few instances in which lesions have occurred at the exact site of an accidental inoculation (de Langen, 1933; Marchoux, 1934; Wayson, 1937). However, even this evidence may not be conclusive. Lepra bacilli have been found in the apparently normal skin of paroled lepers and in the lymph nodes of presumably healthy individuals living in contact with lepers, and therefore it is possible that irritation or trauma of the skin might cause the localization of organisms even in a

(a) *Morphology and Staining* — *M. lepræ* is a non-motile, non-sporogenous, Gram-positive, acid-fast bacillus which varies markedly in size, shape and staining reactions. The bacilli, which are from 0.2 to 0.5 micra wide and from 1.0 to 8.0 micra long, may appear as straight or slightly bent rods with parallel sides and rounded or pointed ends, or they may resemble diphtheroids containing granules or clear spore-like spaces. Branching forms occur, and non-acid-fast Gram-positive granules have been observed free in the tissues. Characteristically the bacilli occur in compact parallel bundles or clumps and in rounded intracellular and extracellular masses or globi. While they are acid-fast and alcohol-fast, their staining reactions are variable, and under certain conditions lepra bacilli may be non-acid-fast. Such changes have been considered as evidence of death of the organisms, but this is questioned as typical acid-fast forms have been found in old putrified tissues. It has been suggested also that alterations in morphology and staining which are especially noticeable during reactionary phases of the disease may represent different stages in the life cycle of the lepra bacillus. In fact, certain observers (Muir and Chatterji, 1933; Rodriguez, Mabalay and Tolentino, 1933; Manalang, 1932) have considered the hypothesis that the infection may be caused by an ultramicroscopic filtrable form of *M. lepræ*.

(b) *Cultivation* — Numerous attempts have been made to grow the lepra bacillus in vitro, and a confusing array of micro-organisms have been isolated from leprotic lesions (see review by McKinley, 1934). For convenience these dissimilar organisms may be arranged in four broad groups as follows: (a) diphtheroids, either non-acid-fast or weakly acid-fast; (b) chromogenic acid-fast bacilli; (c) non-chromogenic acid-fast bacilli; and (d) anaerobic bacilli. Since recognizable leprosy has not been reproduced with any of these organisms, it appears that they may represent either (a) contaminants with no relation to the cause of leprosy, (b) stages in the life history of the true bacillus of leprosy, or (c) organisms whose presence is in some way associated with the true leprosy bacillus which has not yet been cultivated (Topley and Wilson, 1936). There is some indication that the use of tissue culture methods eventually may give more significant results.

(c) *Pathogenicity* — In a few instances the inoculation of *M. lepræ* from human lesions into monkeys has caused localized self-limited inflammatory lesions (Nicholle, 1905; Reenstierna, 1926; Schobl, Pineda and Miyao, 1930), but the typical disease has not been reproduced by experimental methods. Similar inoculations into human beings also have given negative or questionable results. The toxicity of the lepra

bacillus appears to be low if one may judge from the slight general reactions produced in certain patients whose tissues contain enormous numbers of organisms. Little is known concerning immunity to leprosy and such immunological tests that have been used fail to indicate the specific nature of *M. lepræ*.

Pathogenesis

The available information concerning the pathogenesis of leprosy is in many respects inadequate. Experimental attempts to reproduce the disease have failed, the method of its natural transmission is unknown, and the etiological relationship of *M. lepræ* to the disease has been questioned.

Predisposing Factors. — The relatively low incidence of leprosy even among contacts and the lack of toxic symptoms observed in patients with numerous *M. lepræ* throughout the body indicate either that the virulence of the infective organism is low or that the resistance of the average individual usually is high. Epidemiological studies show that the disease is contracted more frequently in certain endemic regions by undernourished individuals of unhygienic habits, especially children, after long contact with infected persons, and that often the early lesions occur on exposed parts of the body.

Portal of Invasion. — The causative organism can enter the body by way of the gastrointestinal, genitourinary or respiratory tracts, but the skin and the nasal mucosa have been regarded as the most likely portals, largely on the assumption that the primary lesions usually occur in one of these tissues. As nasal lesions are common, especially in advanced leprosy, the nose previously was considered an important site of infection (Sticker, 1897; Heiser, 1916), but this is questioned now in view of the observations of Gomez and his associates (192-) and others. Solis and Wade (1925) in a survey of 250 children of leprous patients failed to find *M. lepræ* in the nose prior to skin involvement.

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generalized infection. Moreover the simultaneous appearance of multiple initial skin lesions in different parts of the body, especially when they are precipitated by some other disease or condition, is difficult to explain on the basis of a portal of entry through the skin; so are the many instances in which the first sign of infection is numbness or anesthesia with no evidence of a preceding skin lesion in any part of the body.

Period of Incubation. — The true period of incubation is unknown. It appears that, after the infective agent enters the body, it may be destroyed or eliminated, it may lie dormant for an indefinite period before development, or it may multiply and eventually produce the disease. The time required may be influenced by many factors, including the closeness of contact and the amount and condition of the inoculation, also the age and physical condition of the individual. It has been estimated that the time required for the development of initial lesions subsequent to exposure may be as short as a few months or as long as thirty or more years (Klingmuller), and many observers have reported that the average is about 2 to 4 years.

Evolution of the Infection. — The early lesions of the disease usually consist of minor alterations in the nerves or skin, which are recognized as evanescent neural disturbances and macules, depending on the resistance of the patient. They may disappear spontaneously, may remain inactive and unchanged for long periods of time, or they may continue to develop progressively.

Wade (1935) has suggested that subsequent to this initial stage the evolution of the disease may result either in the benign neural form or the malignant cutaneous form of leprosy as follows: *Benign Neural leprosy.* — The process often starting as described above progresses and causes more marked signs and symptoms, but the patient's resistance continues sufficiently high to limit the spread of the infection in the body and the number of bacilli in the lesions. Both skin and nerves are typically involved, but the neural changes usually predominate sooner or later. Prognosis is relatively favorable as regards overcoming the infection, but permanent mutilations often occur. *Malignant Cutaneous leprosy.* — The infection is relatively unchecked (or the resistance in a benign case breaks down), the bacilli multiplying in great numbers and giving rise to typical lepromatous lesions in the skin and deeper organs. Symptoms of nerve involvement usually arise sooner or later. Prognosis is unfavorable except in the event of effective interference, but occasional cases recover, usually with (secondary) neural residua or sequelae.

Pathology

Leprosy produces pathological changes in many tissues of the body including the nerves, skin and mucous membranes, eyes, lymph glands, testes and other organs. These changes are all based on the development of a characteristic type of granulomatous tissue made up of a loose network of connective tissue cells, which is well supplied with blood vessels and wide lymph channels and is infiltrated with lymphocytes and later with the so-called lepra cells (Fig. [illegible]). The latter are large endothelioid cells packed with acid-fast bacilli and according to C[illegible] (1936) they are undoubtedly histocytes or tissue macrophages, which means that they are currently accepted as originating both locally and also more generally from blood stream or endothelium. The bacilli are not noticeably disintegrated and they apparently cause very little damage to the cell, at least so far as the nuclear material is concerned. Bacilli are found also free in the tissues, and they occur characteristically both inside and outside the cells in brownish granular gloeal masses known as globi which are clumps of organisms inclosed in a capsular material. As the lesion develops the lepra cells slowly become vacuolated, paler staining and larger, eventually producing the typical "foam cells" of Virchow. These may be single or multinucleated and usually contain only a few bacilli which may react abnormally to the acid-fast stain. Some of the more important lesions which may appear in the various tissues are indicated briefly below.

Nerves.—The infective agent has a special affinity for nerve tissue and in practically every case the peripheral nerves are invaded (Fig. 1). The infection may reach the nerve trunks by ascent from cutaneous nerve endings or by means of emboli that lodge in the vasa nervorum and initiate foci which spread up and down through the lymph spaces. In both types of invasion the typical histological changes occur. The early stages are characterized by dilatation of the capillaries, effusion of lymph and a proliferation of connective tissue in which lepra bacilli are scarce and irregularly distributed. Later the bacilli increase and the typical foamy lepra cells appear mainly in the endoneural layer of the sheath of the nerve bundle and in the septa and strands leading into the larger bundles. These changes may produce thickening, local tenderness and rarely abscess formation in the nerve trunks. At first there is considerable swelling, especially in parts subjected to bending or stress, as in the ulnar nerve at the elbow and the external peroneals at the knee, but as the lesion progresses the resulting fibrosis constricts the nerve, reducing its size and causing atrophy of the nerve fibers.

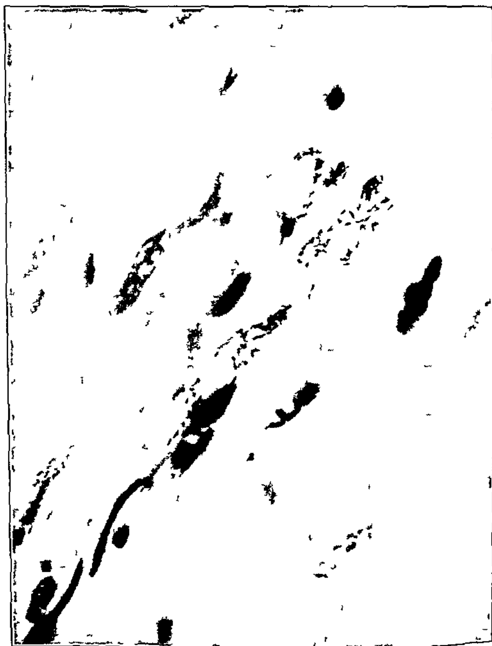


FIG 1 M lepræ in histological section of a nerve (Army Medical Museum Negative No 43687)

The signs associated with nerve lesions may be divided into two groups namely (1) the macular and (2) the acroteric. The *macular* signs which usually result from an ascending type of nerve invasion are characterized by disturbances of pigmentation circulation and sensation in circumscribed areas of the skin. The involvement tends to spread radially as the infection ascends the nerve. *M. leprae* are not found in the affected skin except when the nerve lesion is associated with cutaneous infiltration. The *acroteric* signs which may result from advanced ascending nerve lesions or probably more frequently from metastatic lesions occur in the extremities and have a tendency to centripetal spread. They include alterations of sensation, trophic disturbances in the skin, bones and muscles and paralyses. Lepra bacilli rarely are found in such lesions. The macular and acroteric groups of signs may co-exist and either may predominate.

Skin. — The skin may present a great variety of functional circulatory and structural changes, some of which result from involvement of the nerves while others are due to the development of leprotic * granulations in the corium and the subcutaneous tissue. Such leprotic lesions which are a conspicuous feature of the cutaneous type of leprosy often develop from macules and may occur as infiltrations, nodules and subcutaneous lepromata.

The infective agent may enter the corium either through a break in the surface epithelium or as a capillary embolus from the blood stream. The organisms multiply and eventually may spread laterally and downward producing lesions in the papillary, inter-follicular and sub-follicular layers of the corium or in the subcutaneous tissue, depending on their abundance and the depth of their penetration. (See Fig. 2.)

(1) *Macular Lesions.* — When the papillary layer of the corium is invaded there is perivascular infiltration of small round cells, edema and fibrotic changes which cause flattening of the papillae, obliteration of the inter-papillary spaces and thinning of the epithelium. Viewed externally the lesion resembles the early macule of neural leprosy but may be more hyperemic. It is a circumscribed radially spreading area of skin usually made up of an outer depigmented ring and an inner raised erythematous circle containing a flatter depigmented circle. Only a few lepra bacilli

* The term "leprotic" is applied to those changes which present clinical or microscopic evidence of inflammatory processes, typically of granulomatous nature, which apparently are caused by *Mycobacterium leprae* in them. In such lesions the organism usually can be demonstrated by the ordinary method of examination. The term "leproma" is applied in a general sense to any lesion of a leprotic nature (Leonard Wood Memorial Conference 1933).

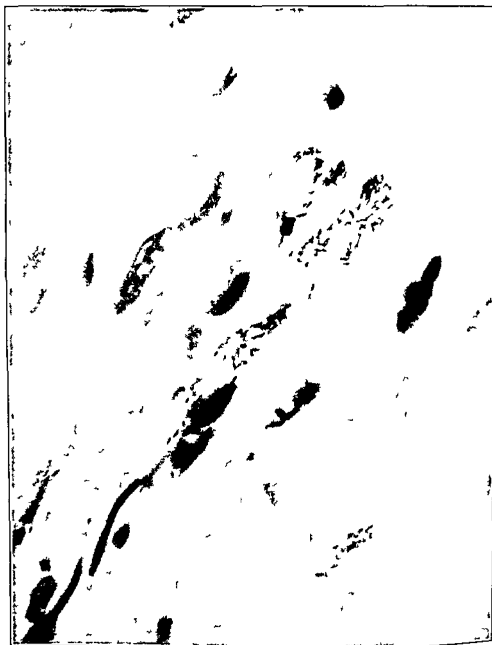


FIG I M lepræ in histological section of a nerve (Army Medical Museum Negative No 43687)

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Fig. 2 M. lepræ in histological section of a leprotic lesion of the skin (Army Medical Museum Negative No 43691)

can be found and usually they are most abundant in the laterally spreading margin of the lesion the resolving central portion often becomes anesthetic and free of bacilli

Infiltrations — As the infection progresses from the macular phase and the lesions become more diffuse and thickened they are designated as leprotic infiltrations When invasion of the interfollicular layer occurs the upward pressure of the granulomatous swelling is resisted by the hair follicles and sweat glands exaggerating the natural folds of the skin The erythematous margins of the surface lesions are more raised than in the papillary lesion and lepra bacilli are numerous Further extension of the lesion into the subfollicular layers of the corium causes upward pressure which obliterates the natural folds of the skin and produces a smooth glossy surface Subsequently due to involvement of the follicles and glands the skin becomes dry and hairless and after resolution it cracks and develops the appearance of crushed tissue paper

(?) *Nodules* – A nodule may be defined as a definitely thickened rounded circumscribed mass of leprotic tissue Nodules may be produced by interference with the radial spread of a diffuse lesion and thus occur within an area of infiltration or they may originate as metastatic lesions in which the invasion of capillary endothelium spreads to the connective tissue around the vessel and produces localized tumor like masses Nodules may occur in the corium or subcutaneous tissue and their size and consistency varies according to the numbers of organisms and the depth of the lesions Soft temporary swellings may appear and last only a few days but usually the nodules are firm and vary from a few millimeters to several centimeters in diameter Later due to the development of fibrous tissue they may become smaller and indurated They contain numerous lepra bacilli and after the initial reaction subsides extensive invasion may occur in the surrounding skin In cases of extreme subfollicular infection the intense infiltration of the skin may produce many rounded and linear nodule like corrugations such as those seen in the face in leontiasis The larger subcutaneous nodular masses often are designated subcutaneous lepromata

Ulcers — The surface epithelium covering leprotic nodules usually is free but because of the swelling it is exposed to trauma and often is the site of injury and ulceration Such ulcers contain great numbers of lepra bacilli and do not heal until all of the leprotic tissue has been removed after which the lesion is closed by extensive scar tissue (Fig .) They differ from trophic ulcers of neural origin which do not show leprotic infiltration

Mucous Membranes — In cutaneous leprosy lesions similar to the

seen in the skin commonly occur in the mucous membranes of the upper respiratory tract The nasal mucosa which has been considered an important portal of infection usually contains lesions at some period of the disease The early changes are characterized by a pale dry mucous membrane in which the bacilli may be scarce or not demonstrable At a later period infiltration nodulation ulceration and scar formation occur in the mucous covering of the septum inferior turbinates or elsewhere and the cartilage of the septum may be perforated or destroyed Lepra bacilli are numerous in these lesions and when ulceration occurs they may be found in the nasal discharges

The membranes of the mouth and pharynx commonly are invaded and are the site of both diffuse and nodular lesions Those of the lips usually are derived from the extension of skin lesions the tongue soft palate and larynx may show infiltration ulceration and subsequent cicatrization resulting in alterations of the voice and obstruction to breathing

Eyes — Lesions of the eye are not uncommon in cutaneous leprosy The infection spreads either through the lymphatics from nearby skin lesions to the conjunctiva and cornea or more rarely through the blood stream to the deeper structures Neural involvement may cause partial paralysis of the orbicularis palpebrarum anesthesia of the cornea and decreased lachrymal secretion and thus expose the eye to injuries resulting in corneal ulceration or other lesions

Lymph Nodes — In practically all cases of leprosy the lymph nodes draining infected parts become swollen and show characteristic leprotic lesions containing large numbers of lepra bacilli The glands most frequently affected are those of the groin axilla the epitrochlear region and the neck

The progress of infection may be illustrated by the inguinal glands when these are affected the lowest node usually is most swollen and shows the most advanced pathological changes the degree of involvement gradually diminishes in the higher inguinal and retroperitoneal nodes until those at the level of the kidney may appear to be normal In active cases the affected nodes are large and on section the cut surface is opaque and yellowish white while in chronic cases they are smaller and show in the cortex deep yellow areas produced by old lepra cells

Testes and Ovaries — In cutaneous leprosy the testicles almost always are affected and lepra bacilli may be abundant in the seminal fluid The tubules are reduced to hyaline strands and are spread apart by leprous granulation tissue containing numerous bacilli During periods of lepra reaction acute orchitis may occur The ovaries are not affected so commonly

Spleen and Liver — In the cutaneous type of leprosy the spleen and liver may show numerous foci of granulation tissue containing many bacilli These lesions are invisible to the naked eye but are quite conspicuous on microscopic examination

Veins — Extensive lesions of the veins may occur in the region of skin *infiltrations especially in the extremities resulting in a thickening of the* vessel wall and a decrease in the size of the lumen

Lung — Occasionally lesions occur in the lungs with signs and symptoms resembling those of pulmonary tuberculosis The sputum is purulent and contains many acid fast bacilli

Bones — The more important changes in the bone consist of the trophic disturbances which are caused by lesions of the nerves however a leprous osteomyelitis may occur (MacCallum 1925) with lesions analogous to those in the skin

Symptomatology

The clinical manifestations of leprosy are extremely variable The early signs and symptoms may be so insignificant that they are overlooked or disregarded by the patient and the infection may remain unrecognized for years or until the lesions become sufficiently extensive to cause the noticeable deformities of the late stages Before outlining the clinical course of the disease brief consideration will be given to its classification and to the cardinal and secondary symptoms

Classification

Leprosy is a general disease and its lesions are never strictly limited *to a single tissue however the organism has a predilection for the peripheral* nerves and when the infection becomes generalized conspicuous lesions occur in the skin Therefore for many years it has been customary to divide cases arbitrarily into three main clinical groups including anesthetic nodular and mixed leprosy which were differentiated according to the extent of the involvement of these two tissues In 1927 Wade and Rodriguez commented on the confusion caused by differences in terminology and application and suggested that only two main types be recognized namely neural and systemic The latter was considered preferable to the term nodular or cutaneous because such cases usually show involvement not only of the skin but of the nerves and other organs of the body

In 1931 the Leonard Wood Memorial Conference adopted a standard

system of classification now in general use which recognizes only two major types of the disease namely (1) *neural* (N) and (2) *cutaneous* (C) and indicates the severity of the process by the symbols N1, N2 N3 and C1 C2 C3 respectively These clinical types and subtypes are defined as follows

Neural type (N) — All cases that show evidence of actual or previous nerve involvement i e alterations of sensation with or without changes in pigmentation and circulation trophic disturbances or paralyses and their consequent results atrophies contractures ulcerations These are not accompanied by leprotic changes in the skin

Neural – 1 (N – 1) Slight neural Cases with one or a few small areas of disturbed sensation which may or may not show alterations of circulation or pigmentation paralyses or trophic disturbances of minor degree

Neural – 2 (N – 2) Moderately advanced neural Cases with extensive or numerous areas of disturbed sensation not confined to any part of the body with paralyses or/and visible evidences of trophic disturbances marked depigmentation moderate atrophy keratosis bullæ etc

Neural – 3 (N – 3) Advanced neural Cases with more or less extensive areas of anesthesia and marked motor and trophic disturbances marked paralyses atrophies contractures trophic ulcers and mutilations

Note Wade (1935) has suggested that the so called tuberculoid form of leprosy is a variety or subtype of the neural (N) type and that it might be designated by the symbol Nt

Cutaneous type (C) — All cases showing leprotic lesions in the skin Such cases may or may not show at any time clinical manifestations of nerve involvement

Cutaneous – 1 (C – 1) Slight cutaneous Cases with one to a few leprotic macules or a few small areas of infiltration or nodules

Cutaneous – 2 (C – 2) Moderately advanced cutaneous Cases with numerous leprotic macules or fairly numerous or marked areas of infiltration or nodules frequently with lesions of the mucosa

Cutaneous – 3 (C – 3) Advanced cutaneous Cases with numerous or very marked leprotic lesions in various stages of development or retrogression usually with lesions of the mucosa In all cutaneous types there may be varying degrees of neural involvement and such cases should be recorded to indicate the degree of this involvement as for example C – 2 N – 1

Secondary neural Neural cases that were formerly cutaneous but from which the active leprotic lesions have disappeared

Cardinal and Subsidiary Symptoms

Many ca es of leprosy regardless of type sooner or later may become mixed and sho evidence of both nerve and sl in involvement therefore the important clinical sign may be considered together Wade and Rodriguez separate the more characteristic ones into two groups as follows (1) the principal or cardinal symptoms one of which must be present befo e the clinical diagnosis can be made and (2) the secondary or subsidiary ones which are not diagnostic but may help to corrobor ite the diagnosis

Cardinal Symptoms

Anesthesia — Frequently the first clinical manife tation observed is a mall area of superficial anesthesia which may or may not be preceded or accompanied by parasthesia or by visible lesions of the skin Such an anesthetic area may be the only evidence of infection fo several months or years during which time it gradually spreads and progresses causing first the loss of thermal sensibility then loss of the sense of pain and eventually loss of the superficial tactile sense The deep or mu cle sense is retained but the ane thesia becomes complete The affected areas may be small and isolated due to the invasion of nerve terminals but as a rule they become exten ive and correspond roughly with the distribution of the superficial nerves

Skin Lesions — The characteristic lesions of the skin include macules infiltrations nodules subcutaneous lepromata and papules

Macules not uncommonly are the first evidence of the disease e pecially in children and they may be the only outward manifestation for year Macules of the neural type may be evanescent and darker than the normal kin they show di turbances of sensation and are bacteriolog ically negative As they become more prominent they pread periph erically and ultimately they may disappear leaving the skin atrophied and anesthetic The cutaneous macule becomes more elevated and reddish in color and sooner or later lepra bacilli may be found in the rai ed erythematous non anesthetic portions

Infiltrations and *nodules* are fairly early skin lesions produced by the deposit of leprotic tissue and numerous lepra bacilli As the infiltrated lesion progresses the natural folds of the skin first are exaggerated and later obliterated producing a tense smooth and glistening surface Nodular masses may appear in the diffuse infiltrated areas or elsewhere or the entire area may become extensively involved showing many

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Secondary neural Neural cases that were formerly cutaneous, but from which the active leprotic lesions have disappeared

Prodromata — The period preceding onset often is characterized by such prodromal symptoms as occur in other chronic infections These include gastrointestinal abnormalities malaise headaches muscular and neuritic pains and other transient neural disturbances some of these may remain after the disease becomes apparent clinically Attacks of fever and weakness may recur at irregular intervals for several years and it has been suggested that these prodromal febrile reactions may be caused by the dissemination of the infection throughout the body

Onset of the Disease — The infection may begin insidiously with little or no general toxic or inflammatory reaction or it may start with severe attacks of fever accompanied by toxemia erythematous rashes and pains in the nerves No uncommonly the onset is precipitated by (a) other diseases such as syphilis and malaria (b) puberty childbirth the menopause or (c) environmental or dietary changes

Initial Signs and Symptoms — The early clinical manifestations may include a great variety of minor localized changes such as disturbances of sensation circulation or pigmentation weakness or paralyses and minimal trophic changes Macules or small areas of infiltration or nodulation may be the first sign observed

From a survey of [illegible]30 adult lepers in the Philippines Wade and Rodriguez (19[illegible]7) concluded that the earliest lesions were as follows paresthesia 34 per cent localized anesthesia 11 per cent hypopigmented macules 13 per cent red macules and infiltrations which often were accompanied by nosebleed and malaria like fevers 27 per cent Less frequently the first symptoms noticed by the patient were generalized papular eruptions 4 per cent bleb formation usually about the knees and on the plantar surfaces 2 5 per cent persistent nosebleed and coryza 1 per cent scaling of the legs 1 per cent plantar ulcers 1 per cent In children the most common initial sign was the hypopigmented macule

The latter observation conforms with the results of studies of early lesions in children born of leper patients in the Philippines made by Gomez and associates (19[illegible]) Rodriguez and associate (1926–1935) Lara and de Vera (1935) and Chiyuta (1933–1935) Their work indicates that the initial lesion may occur at the early age of one or two years and that it usually consists of one or more macules which appear as hazy areas of depigmented skin usually do not contain demonstrable bacteria are frequently associated with disturbances of sensation and may or may not disappear Chiyuta observed that the macule may be preceded or replaced by a papular or goose flesh type of eruption

In 1936 Wayson in Hawaii reported the result of a three year study

elongated nodule like thickened folds irregularly separated by depressions that probably represent the former natural lines of the skin

Subcutaneous lepromata appear in advanced cases and a e firm deep seated tumor like masses of leprotic tissue Like the more superficial nodules they may remain unaltered for long periods and slowly become fibrotic and indurated The overlying skin remains free but often is the site of injuries resulting in ulcers which heal with scar formation

Red papules occur as small solid painful and tender leprotic eleva tions not more than 5 mm in diameter They may appear early in the disease or subsequently during lepra reactions and not uncommonly are observed in cases undergoing treatment

Subsidiary Symptoms

Parasthetic symptoms are frequent subsidiary manifestations in a large proportion of cases They may be associated with vascular disturbances and with weakness or paralysis of certain muscles

Thickening of peripheral nerve trunks may occur at an early stage of the disease

Non inflammatory enlargement of lymph glands always occurs in cuta neous leprosy and often in the neural type The individual nodes remain intact are movable and show no other evidence of inflammation but during periods of lepra reaction they become tender and may even sup purate

Anhydrosis loss of hair and *icthyosis* frequently occur especially on the legs

Ulceration of the nasal mucosa may occur early and cause destruction of the cartilage of the septum resulting in loss of the tip of the nose

Trophic changes such as the atrophies contractures ulcers and other mutilating lesions really are sequels of leprosy

Clinical Course

The clinical course of leprosy is irregular being characterized either by slow or rapid development which may be delayed by periods of in activity or of transient or long continued recession The progress of the disease is influenced in some unknown way by the so called lepra re actions , which may be followed either by an advance of the process or by improvement As previously indicated the infection may stop at the stage of prodromal or initial symptoms or it may continue and cause either the relatively benign neural type of the disease or the malignant cutaneous type

Prodromata — The period preceding onset often is characterized by such prodromal symptoms as occur in other chronic infections These include gastrointestinal abnormalities malaise headaches muscular and neuritic pains and other transient neural disturbances some of these may remain after the disease becomes apparent clinically Attacks of fever and weakness may recur at irregular intervals for several years and it has been suggested that these prodromal febrile reactions may be caused by the dissemination of the infection throughout the body

Onset of the Disease — The infection may begin insidiously with little or no general toxic or inflammatory reaction or it may start with severe attacks of fever accompanied by toxemia erythematous rashes and pains in the nerves Not uncommonly the onset is precipitated by (a) other diseases such as syphilis and malaria (b) puberty childbirth the menopause or (c) environmental or dietary changes

Initial Signs and Symptoms — The early clinical manifestations may include a great variety of minor localized changes such as disturbances of sensation circulation or pigmentation weakness or paralyses and minimal trophic changes Macules or small areas of infiltration or nodulation may be the first sign observed

From a survey of 230 adult lepers in the Philippines Wade and Rodriguez (19 7) concluded that the earliest lesions were as follows paresthesia 34 per cent localized anesthesia 11 per cent hypo pigmented macules 19 per cent red macules and infiltrations which often were accompanied by nosebleed and malaria like fevers 27 per cent Less frequently the first symptoms noticed by the patient were generalized papular eruptions 4 per cent bleb formation usually about the knees and on the plantar surfaces 2 5 per cent persistent nosebleed and coryza 1 per cent scaling of the legs 1 per cent plantar ulcers 1 per cent In children the most common initial sign was the hypo pigmented macule

The latter observation conforms with the results of studies of early lesions in children born of leper patients in the Philippines made by Gomez and associates (192) Rodriguez and associates (1926–1935) Lara and de Vera (1935) and Chiyuta (1933–1935) Their work indicates that the initial lesion may occur at the early age of one or two years and that it usually consists of one or more macules which appear as hazy areas of depigmented skin usually do not contain demonstrable bacteria are frequently associated with disturbances of sensation and may or may not disappear Chiyuta observed that the macule may be preceded or replaced by a papular or goose flesh type of eruption

In 1936 Wayson in Hawaii reported the results of a three year study

of 108 children of various ages from a few months to 16 years, who at birth or soon thereafter had been separated from their leper parents and kept under medical supervision At one time or another thirty five of the children showed minor, non-diagnostic, disturbances of the smaller twigs or branches of the peripheral or sympathetic nerves and ten of these eventually developed combinations of signs that justified a clinical diagnosis of leprosy Five of these ten cases were found to be bacteriologically positive for *M lepræ* one at the beginning of symptoms and the others after periods lasting from several months to two years In nine of the cases the incidence of various early subsidiary clinical signs was as follows lagopthalmos 8 droop of the angle of the upper lip 8 atony or slight atrophy of the interosseous muscles or of the thenar or hyperthenar eminences 6 paresis or paralysis of the lumbrical or interosseous muscles of the hand 1 thickened nerve trunks or branches auricular ulnar or peroneal or, in one case, supraclavicular 9 trophic disturbances dryness or anhidrosis scaliness, glossiness or wrinkling in one or more areas of the skin other than in definitive lesions 5 sensory disturbances in one or more areas of the skin without definitive lesions 5 circumscribed or definitive skin lesions (macules) 4 sensory changes in one or more macules 4 From this study it was concluded that —in the early stages of the disease there may be only minor neurological findings and that the skin lesions which may or may not be evident in these stages are often of short duration and cannot be regarded as specific for leprosy

The primary macular eruption occurs most frequently on the face especially the superciliary region the nose cheeks and ears the extensor surfaces of the limbs the backs of the hands the back buttocks (Fig 3) and chest The palms of the hands and the soles of the feet rarely are attacked (Manson Bahr) It has been suggested that the character of the macules may indicate the subsequent type of the disease the depigmented or hyperpigmented ones preceding nerve leprosy and the more hyperemic ones resulting in cutaneous leprosy (Klingmuller 1930)

As the disease progresses a deposit of leprotic granulation tissue occurs which if limited to the nerves causes neural leprosy or if it also involves the skin and other organs produces cutaneous leprosy

Neural Leprosy

The neural type (Figs 4 and 4(a)) of leprosy is characterized by a long prodromal period a slow afebrile onset and a chronic course which lasts for an average of about eighteen years or longer with a tendency to spontaneous recovery The symptoms are those of a multiple neuritis

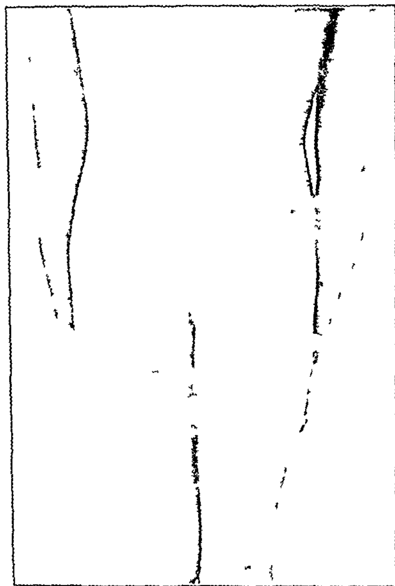


Fig 3 The early macular stage of leprosy (Army Medical Museum Negative No 39411)

with extensive trophic changes, and there are no leprotic lesions in the skin. Some observers claim that the nasal mucosa may contain lepra bacilli.

The first symptoms are due to involvement of the smaller divisions of the peripheral nerves, especially the ulnar, great auricular and the

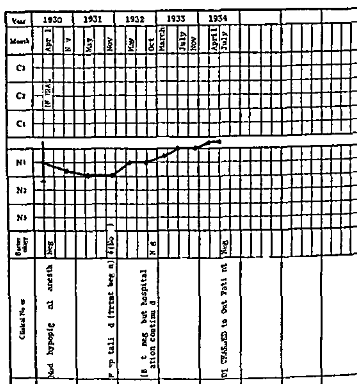


Fig. 4. Neural Leprosy (From Wade and LeRoux 1935, Case No. 1). Representing a neural case seen early with only a few hypopigmented anesthetic spots. Being a casual out patient he was untreated for some time during which there was little change. The nasal mucosa then was found bacteriologically positive and treatment was started. The nasal lesion cleared up, the other manifestations slowly disappeared and the patient was discharged as fully arrested without sequelae.

peroneal. There are darting pains in the nerves, evanescent disturbances of sensation, circulation and pigmentation in small circumscribed skin areas, weakness, paresis or atrophy of small groups of subjacent muscles and minimal trophic lesions. The macules become hyperesthetic and anesthetic and may disappear after a time, or they may persist and spread forming large, round, oval or serpiginous lesions resembling ringworm.

This mild stage may last for years before the more typical signs of nerve leprosy develop

As the infection advances the nerve trunks become more swollen tender and painful and the neurological signs increase correspondingly

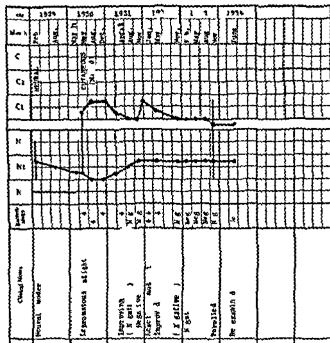


Fig. 4a Neural Leprosy (From Wade and LeRoux 1935 Case No 3) A neural case which developed lepromatous lesions of the skin Under treatment these cleared up temporarily relapsed later but ultimately disappeared The patient was released with only moderate neural sequelæ

The areas of disturbed sensation spread become more numerous and are not confined to any part of the body with paralyses and often with visible evidence of trophic changes such as marked pigmentation moderate atrophy keratosis and bullæ The bullæ (pemphigus lepræ) which are distinctive of the disease may occur singly or as a series of blebs on the hands feet knees or elsewhere They vary markedly in size and contain a clear serous fluid After a few days they rupture exposing a reddish surface which rarely ulcerates and later becomes a pale possibly anesthetic spot with a pigmented border

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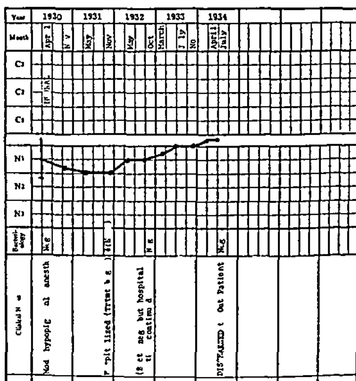


FIG 4 Neural Leprosy (From Wade and LeRoux 1935 Case No 1) Representing a neural case seen early with only a few hypopigmented anesthetic spots Being a casual out patient he was untreated for some time during which there was little change The nasal mucosa then was found bacteriologically positive and treatment was started The nasal lesion cleared up the other manifestations slowly disappeared and the patient was discharged as fully arrested without sequelæ

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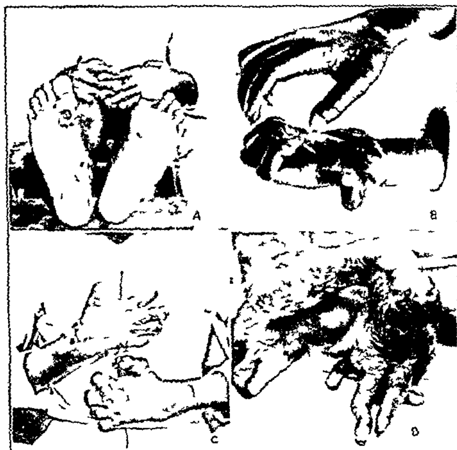


Fig 5 *a* Leprosy neural type early typical perforating ulcer due to traumatism of anesthetic tissues (Photograph by Dr O E Denney) *b* Leprosy neural type moderately advanced The claw hand or *main en griffe* (Army Medical Museum Negative No 39 50) *c* Leprosy neural type advanced claw hands with considerable traumatic ulceration and some distortion due to leprous osteitis (Photograph by Dr O E Denney) *d* Leprosy neural type advanced extreme contracture and scarring (Army Medical Museum Negative No 34235)

Cutaneous Leprosy

The cutaneous type is characterized by typical lesions of the skin with involvement of the other tissues of the body especially the mucous membranes lymph glands and nerves It is more acute and malignant than the neural type its course is shorter averaging about eight years

Eventually the nerve involvement reaches an advanced stage characterized by extensive areas of anesthesia and severe motor and trophic disturbances The skin changes may or may not persist and the lymph glands usually are enlarged The anesthesia frequently occurs symmetrically on the feet thighs hands arms forearms and face and later may affect the trunk As it becomes more complete the affected parts commonly are injured resulting in ulceration Along with the anesthesia there may be atrophy and weakness of subjacent muscles resulting in characteristic distortions of the extremities and face For example atrophy of the muscles of the forearm followed by involvement of the thenar and hypothenar eminences and the interossei causes contractures of the fingers resulting in the so called "claw hand" (Fig 5) Similar changes occur in the legs and feet

Other muscles may become affected as in progressive muscular atrophy which condition however does not cause superjacent anesthesia Involvement of the facial muscles especially those about the eyes and mouth causes a characteristic leering masklike appearance Eventually it becomes impossible to close the eyes the upper lid droops the lower is everted and the eyeball may become fixed

The secretion of tears stops the conjunctiva becomes dry and thickened and the cornea may become ulcerated or leucomatous resulting in blindness Ulcerations and loss of the nasal septum may occur as in the cutaneous type resulting in destruction of the tip of the nose The lips may be paralyzed the gums may retract and the teeth fall out paralysis or anesthesia of the buccal structure may interfere with eating or articulation

Atrophic areas of thinned skin on the extremities may result in an ichthyotic appearance due to the formation of long cracks The nails become distorted or atrophied and hook shaped Trophic ulcers appear on exposed parts of the extremities being especially common on the sole of the foot (Fig 5) and may penetrate the joints causing the loss of fingers or toes

The loss of digits also may be caused by dry gangrene or by a trophic absorption of the phalanges in which the shaft is lost more rapidly than the articulating portions of the bone As this process continues the fingers or toes may become completely absorbed and frequently the nails remain attached to the mutilated stumps

In spite of the repulsive lesions seen in patients with advanced neural leprosy these individuals may live for periods of 18 to 20 years and usually they die of some other disease such as tuberculosis nephritis pneumonia or dysentery

the invasion may originate in the iris or ciliary body and eventually cause blindness and destruction of the eyes The cutaneous type of leprosy practically always is accompanied by nerve involvement therefore if the patient survives the above distressing lesions he is subjected

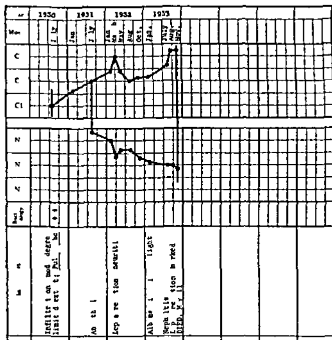


Fig 6 Cutaneous Leprosy (From Wade and LeRoux 1935 Case No) Illustrating an early cutaneous case of rapid course not treated because of complicating tuberculosis Neural manifestations appeared the case becoming mixed Marked lepra reaction occurred with extension of the disease followed by rapid and fairly marked improvement which however was only temporary persistent lepra fever developed with extreme lesions and the patient died nephritis developed toward the last This case shows how irregularities and sudden events are charted

to the additional burden of the advanced signs and symptoms mentioned in the discussion of the neural type (Fig 6) In some instances the skin lesions may recede either spontaneously or subsequent to treatment and a cutaneous case may result in the so called burned out or secondary neural type of leprosy

and it usually terminates fatally unless it can be treated effectively Prior to onset there may be a period of prodromal symptoms lasting a few weeks months or years which is characterized by epistaxis diarrhea mental depression malaise anorexia headaches various sensory disturbances or sweating and by attacks of intermittent fever preceded by chills and followed by prostration The disease may be first recognized during such a febrile attack by a diffuse erythematous eruption or by macules on the face extremities buttocks or elsewhere The lymph nodes become enlarged As the fever subsides the eruption usually disappears but in many instances the macules remain and develop into small leprotic infiltrations which may be felt as thickened areas of skin At irregular intervals new crops of macules and infiltrations occur their appearance often coinciding with a recurrence of the febrile reaction At such times the older lesions become more active and spread rapidly producing more extensive leprotic deposits The covering skin surface is smooth and shiny and of a red or pink color which later fades to a dirty yellow It is devoid of hair has a greasy appearance is fairly firm and usually is freely movable

As the disease becomes moderately advanced it is characterized by numerous leprotic macules or by fairly numerous or marked areas of infiltration or nodulation frequently with lesions of the mucosa Subsequently all the signs become more advanced and extensive leprotic lesions in various stages of development and retrogression appear over the skin and usually in the mucosa The lesions are most common on the extremities and the face where they occur on the forehead cheeks alæ of the nose lobules of the ears lips and chin The hair of the eyebrow beard and moustache drops out and due to the fusion of many infiltrative lesions the entire skin surface of the face may be thrown into thick nodule like corrugations separated by irregular furrows This produces the grotesque condition seen in late leprosy known as leontiasis (see Fig 7) Similar changes may occur elsewhere

The nodules have a tendency to central softening and may be absorbed leaving a smooth circular area of scar tissue or they may produce extensive ulcerations which discharge a sticky yellowish pus Infiltrations in the nasal mucosa cause ulcerations and loss of the cartilage of the septum resulting in a foul discharge These and similar lesions in the pharynx tongue glottis and epiglottis may result in loss of the senses of smell and taste interference with articulation and chewing and obstruction to breathing sufficient to necessitate tracheotomy The eyes also become invaded by the leprotic growth extending from the skin to the conjunctiva and cornea and possibly into the interior chamber or

Complications

Some of the more important sequels of leprosy include mutilations blindness asphyxiation due to obstructing lesions or edema of the glottis pyogenic infections amyloidosis chronic gastrointestinal disturbances and nephritis Tuberculosis and pneumonia frequently occur as complications and the former is the most common cause of death Syphilis yaws malaria dysentery or other diseases including parasitic infections often occur in leprous patients and may exert an important influence on the progress of the disease

Lepra Reaction

An important factor in either type of leprosy is the so called lepra reaction which frequently is referred to as an acute exacerbation of the disease These reactions are of common occurrence and may vary in severity from a painful neuritis or the reddening of an isolated skin lesion to a general eruption or a sudden marked increase in the severity of all existing lesions with fever and toxemia which in some instances may be followed by death

Gay (1935) summarized observations made on lepra reactions at Culion as follows Fever remittent or intermittent is common but may be absent In the cutaneous type new areas of redness and erythema appear within a few days or even hours are characterized by tenderness and do not at first have the histological character of the old slowly formed nodules These new lesions may contain large numbers of acid fast bacilli almost immediately The old nodules less frequently show reactivation Both old relighted and new lesions may occur Although the leucocyte count shows no change in leprosy from the normal there is a sharp total and relative increase of the neutrophiles during the acute lepra reaction (Badger)

In the nerve type of leprosy the symptoms include fever a painful neuritis with at times new macular spots Conjunctivitis iritis and rheumatoid symptoms both arthritic and muscular occur Orchitis and swelling of lymph nodes are not infrequent

The lepra reaction occurs once or many times and is acute sub acute or prolonged in its course The effect of the reaction on the course of the disease is debatable Not infrequently the newly awakened or re activated lesions disappear with a return of the patient to a greatly improved or what appears to be a normal condition At other times the symptoms and lesions grow progressively worse



FIG 7 *a* Leprosy cutaneous type fairly early numerous miliary nodules scattered over entire face moderate diffuse thickening in superciliary region nasal alæ and ear lobules (Photograph by Dr O F Denney) *b* Leprosy cutaneous type moderately *advanced* (Army Medical Museum Negative No 43453) *c* Leprosy cutaneous type moderately advanced diffuse thickening of dermal tissues of entire face giving rise to *leontiasis* (Photograph by Dr O F Denney) *d* Leprosy cutaneous type advanced diffuse infiltration of tissues and some superficial ulceration saddle nose from destruction of nasal cartilages pendulous ear lobules (Photograph by Dr O E Denney)



FIG 8 Tuberculoid Leprosy (From Wade H W 1934)

No 8 Extensive macules edges very irregular zones narrow and finely nodulate On neck are c rc nate lesions. No 9 Extensive compound macules very irregular in width markedly papillate No 10 Relapse of supposedly healed lesions A narrow active zone of sl ght infiltration and moderate erythema just outside of the border of a previous paler area (The scars are due to native treat ment)

TUBI RCULOID LEI ROSY

Tuberculoid leprosy is regarded by Wade (1935) and others as a variety of the neural type It is characterized by the appearance of tuberculoid skin lesions which are more sharply limited and less diffused than are typical leprotic infiltrations (Fig 8) The lesions show less marked sensory changes than do the simple neural leprides contain few or no demonstrable lepra bacilli histologically are not lepromatous and are characterized by epitheloid cell foci and often by giant cells of the Langerhans type According to Wade Hayaski was able to differentiate tuberculoid and cutaneous type infiltrations with the so called leprolin test and it has been reported that cases with tuberculoid lesions give even stronger reactions than do ordinary neural cases

DIAGNOSIS

The early diagnosis of leprosy is of importance both from the viewpoint of preventing its spread to others and of affording relief to the patient Advanced cases are easily identified but considerable diagnostic skill may be required for the recognition of the minor subsidiary manifestations which precede the appearance of the cardinal signs

Methods of Examination — In the report of the Leonard Wood Memorial Conference (1931) it was recommended that in addition to the many auxiliary tests available special importance should be attached to the methods of examination briefly indicated below for the recognition of anesthesia and of leprotic lesions

Clinical Examination — The entire body should be examined in a good light and all tests for sensation should be made with the patient blindfolded

(a) *Sensation to Light Touch* — First test the normal skin repeatedly with some light object such as a cotton swab feather camel s hair brush or a piece of paper and have the patient indicate with the finger the places touched After the patient responds normally test the suspected area similarly and map out the anesthetic areas

(b) *Sensation to Pain* — The test for pain is carried out under similar conditions except that the skin is alternately touched with the head of a pin and pricked with the point

(c) *Sensation of Heat and Cold* — The suspected areas may be touched alternately with two test tubes one containing hot (40°–50 C) and the other cold water (20° C or lower) the patient being asked to distinguish between them

minutes at room temperature or for three minutes during which it is heated just sufficiently to produce steam Then wash and decolorize with sulphuric acid (10 per cent) or nitric acid (10 to 20 per cent) counterstain with methylene blue and examine for *M lepræ* Gabbett s methylene blue may be substituted for decolorization and counterstaining Should there then be any question as to the identity of acid fast organisms seen in the stained smears histological sections should be examined and saline suspensions of the infected tissues should be inoculated into guinea pigs to rule out the presence of *M tuberculosis*

Aids to Diagnosis — In addition to the subsidiary clinical signs various procedures have been used in the attempt to facilitate the diagnosis Potassium iodide has been administered for the production of local or general provocative reactions which may assist in the recognition of doubtful cases No specific serological test of practical value has been developed It is claimed that the Wassermann and Kahn tests may be positive in certain cases of leprosy even when syphilis is not present but the exact significance of such tests is unknown (Soule 1935) The ordinary clinical examinations of blood and urine may show changes produced by the complicating conditions but none that are diagnostic of leprosy The erythrocyte sedimentation rate may be increased slightly during neural leprosy and definitely increased in the cutaneous type Some importance has been attached to this test but its diagnostic value has been questioned The histamine test used by Rodriguez and Plantilla (1931) may serve to indicate anesthetic areas not detectable otherwise the flare which this substance produces being absent in the normal skin Chiyuto (1932) concluded that the test has only a relative value being positive when tuberculoid changes have taken place or the area is anesthetic but that it is not dependable in the early stages when there is only perivascular infiltration without neurological changes

Skin tests based on the intradermal inoculation of sterile suspensions of leprotic tissues have been used by various workers (Teague 1909 Mitsuda 1923 Chiyuto 1932 Hayashi 1933 Muir 1933 Dubois and Degotte 1934 Montanes 1933 etc) It has been observed that injections of Mitsudas leprolin cause indurated lesions in most healthy adults and in children of more than three years of age that it produces similar reactions in a smaller percentage of patients with neural leprosy and that the test usually is negative in healthy infants and in patients with cutaneous leprosy Its value as a diagnostic test has been questioned but it may prove to be useful in determining the results of treatment

Differential Diagnosis — Leprosy has been confused with various

(d) *Thickening of the Skin* — Inspection with or without a magnifying glass should be supplemented by palpation the suspected area being rolled between the finger and thumb Comparison should be made with the surrounding skin and with corresponding areas on the other side of the body

(e) *Mucous Membranes* — In examining the mucous membrane a speculum should be used and the field should be well illuminated

Bacteriological Examination — Material for bacteriological examination should be collected from several sites At times organisms may be demonstrable only in smears from one lesion or one portion of a lesion In neural cases the bacilli rarely are found in the skin lesions in early cutaneous cases the skin lesions may contain only a few scattered bacilli which later become more numerous and generalized or may decrease if the case improves The smear should be as free as possible from blood or serum but should be so collected as to contain cellular material from the deeper tissues

(a) *Skin specimens* may be collected either by the 'scraping or snip method In the former a scalpel is used to make a small incision about 2 millimeters deep well into the dermis and material scraped from the deeper part is smeared on a clean bacteria free glass slide In the snip method a small portion of dermis at least 2 mm thick is obtained with a sharp pair of scissors curved on the flat and the cut surface of the tissue is pressed firmly on the slide so as to express as much of the cellular material as possible Specimens should not be taken from anesthetic areas although a few organisms may be found in the raised erythematous non anesthetic margins of such lesions Usually they are numerous in leprotic infiltrations in any part of the body, and a favorable site is the lobe of the ear Bacilli are abundant in true leprotic ulcers but are rare in trophic or other types of ulceration

(b) *Nasal specimens* may be collected with a blunt narrow bladed scalpel by scraping the mucosa deep enough to cause slight bleeding Using a nasal speculum and good illumination, collect material from any infiltrations nodules or ulcers present If no lesion is found scrape the mucosa of the septum inferior turbinates and the floor of the nose This material should be smeared on clean glass slides

(c) *The staining* of the smears as recommended by the Leonard Wood Memorial Conference (1931) is carried out as follows Dry in the air and fix by passing over a flame Cover with a solution of carbolfuchsin (prepared by mixing one part of a 10 per cent solution of basic fuchsin in 90 per cent alcohol with nine parts of a 5 per cent solution of carbolic acid crystals in distilled water) and allow the stain to act either for 10

sical agents in an attempt to stimulate general healing and to cause the resolution of individual lesions It is considered important to begin treatment as soon as possible as the best results have been obtained in early cases The drugs most commonly used at present are oils of the chaulmoogra group (obtained from the seeds of *Taraktogenos kurzii* *Hydnocarpus wightiana* or *H anthelmintica*) or their derivatives especially the ethyl esters and the sodium salts of the respective fatty acids

The pure oil has been used widely for oral administration and for subcutaneous and intramuscular injection It causes less reaction than the derivatives and therefore may be preferable for cases complicated by nephritis or tuberculosis provided these conditions are slight and non progressive and the treatment is used with caution When given by mouth the dose may be from 5 to 60 drops three times daily (Meakins 1936) and any desirable vehicle may be added Patients frequently complain however of gastric irritation and nausea and because of this it may become necessary to resort to another method of administration According to the so-called Mercado method a mixture containing 60 c c (ʒ–) each of chaulmoogra oil and camphorated oil with 0 23 gm (gr 60) of resorcin may be used for intramuscular injection in doses of 0 3 to 3 0 c c two or three times a week This causes some pain and the results have not been entirely satisfactory A mixture of hydnocarpus oil and 4 per cent creosote has been preferred for routine use by some leprologists The sodium salts of the fatty acids such as alepol also have been popular Alepol is a powder which can be dissolved in distilled water sterilized and inoculated Its use causes some pain

In certain large treatment centers such as Culion the ethyl esters are preferred As a rule they are combined with 0 5 per cent of metallic iodine to decrease their irritant action The iodized preparation is a dark brownish oily fluid which is moderately thick but can easily be injected through a 20 gauge needle Usually it is administered both intramuscularly in the buttocks and intradermally in the skin lesions It is given at weekly intervals and as a rule not more than 5 0 c c (ʒ 1¼) should be given to any patient at one time and not more than 0 1 c c (minim 1½) should be injected at any one point in a lesion It is well to begin with a total dose of 0 25 to 0 5 c c and to increase this by 0 5 c c each week until the maximum tolerated amount is reached The patient should be watched carefully for signs of intolerance such as reactions with indurations temperature over 100 F pains in the chest dizziness etc or progressive loss of weight If such adverse signs appear the treatment should be discontinued for one or two weeks and then recommenced with smaller amounts which should be increased more

other diseases including tuberculosis syphilis, yaws blastomycosis and other mycotic infections erythema nodosum erysipelas kala azar beri beri syringomyelia and other conditions These diseases may be differentiated by their typical signs and symptoms supplemented by diagnostic or therapeutic tests and by the demonstration of the respective specific organisms

PROGNOSIS

The prognosis in leprosy usually is unfavorable However the disease is subject to periods of spontaneous improvement and according to Rogers and Muir (1928) and others it has a tendency toward self healing Since the time of Hansen and Looft (1895) it has been observed that neural leprosy often dies out and that infrequently the cutaneous type may do likewise Nevertheless the probability of a permanent cure in untreated cases is slight and the disease may recur after long periods of improvement The neural case may last for an average period of eighteen years and the cutaneous for about eight years and during this time considerable relief may be afforded by treatment Leprosy patients are unusually susceptible to intercurrent infections which are commonly the cause of death

TREATMENT

The modern treatment of leprosy consists of the use of various preparatory general and special measures which should be adapted to the needs of the individual case and should not be applied indiscriminately

Preparatory Treatment — Prior to the use of special antileprosy treatment the patient should be examined thoroughly for complicating diseases such as syphilis yaws tuberculosis malaria intestinal infections mycoses etc When present these conditions should be treated and eliminated if possible as otherwise they may interfere with the patient s response to the drugs used for his leprotic infection

General Measures — Every effort should be made to improve the patient s general physical and mental condition and thus prepare him to withstand the long course of special treatment This may be accomplished as in other chronic diseases by providing facilities for good personal hygiene a well balanced diet supervised exercises occupational therapy and various other activities that stimulate morale

Special Treatment — The special measures used for the treatment of leprosy include the administration of certain drugs and the use of phy

indication a sharp purgative is given means being taken thereafter to keep the bowels well regulated

(b) A light but well balanced nutritious diet should be given

(c) Accompanying diseases should be searched for and treated The presence of such diseases though often obscure may stimulate a lepra reaction

(d) Potassium antimony tartrate given every second day intravenously in doses of 0 02 to 0 04 gram has been found useful

(e) Calcium chloride (10 cubic centimeters of a 5 per cent solution) may be given intravenously

(f) Calcium lactate 1 to 2 grams daily in divided doses and sufficient sodium bicarbonate may be given to make and maintain an alkaline reaction in the urine

(g) Lepra reaction may be accompanied by a very painful neuritis which may lead to rapid atrophic changes in the parts supplied by the affected nerves Rapid relief of pain may be afforded by the intramuscular injection of adrenaline (0 3 cubic centimeter of a 1 to 1 000 solution) diluted in saline or by the administration orally of 0 05 gram of ephedrine sulphate The effect of the latter drug is more lasting than that of the former Instantaneous relief has also been obtained by the injection around a subcutaneous nerve trunk of 10 cubic centimeters of 0 05 gram of ephedrine sulphate dissolved in saline

In giving special antileprosy treatment care should be taken not to exceed the tolerance of the patient otherwise lepra reaction may result Such special treatment should always be discontinued during lepra reaction and until the patient has completely recovered therefrom

Local Treatment of Leprotic Lesions — Lesions have been treated locally by various methods which cause counter irritation including inunctions of oils and ointments applications of caustics such as a 1–5 solution of trichloracetic acid use of the thermal cautery or applications of carbon dioxide snow for 20 to 90 seconds Lesions of the nasal mucosa may be treated with chromic acid either solid or in 5 to 60 per cent solution or by fulguration with a diathermy apparatus

Surgical Treatment — Operative procedures often are required for the correction of complications and sequelæ In a few instances small initial lesions have been excised in the attempt to stop the progress of the disease Large nodules may be removed surgically or with the thermo cautery Ulcers may be scraped to remove leprotic tissue Perforating ulcers of the foot when due to the presence of dead bone usually heal after removal of the bone Tracheotomy may be required for respiratory obstruction and various operations may be necessary on the eye

slowly and not carried to the previous maximum According to Wade and Rodriguez (1927) the total dosage appropriate for patients in the different age groups is as shown in table II

TABLE II

Dose by Age of Chaulmoogra Oil and its Esters

Age	Ethyl Esters with ½ per cent Iodine	Purified Chaulmoogra Oil
	c c	c c
To 3 years	1	1–2
3 to 6 years	2	2–3
5 to 15 years	3	3–5
Over 15 years	4–6	5–10

Intradermal Infiltration —When possible the lesions should be completely infiltrated by the intradermal injections and if they are too small to accommodate the total dose the remaining portion of the drug should be given intramuscularly The frequency of the inoculations in any lesion should be determined by the degree of the local inflammatory reaction

Contra indications to Chaulmoogra Oil and its Derivatives —Neither chaulmoogra oil nor its derivatives should be given to patients who have advanced pulmonary tuberculosis acute or advanced chronic nephritis or to anemic debilitated individuals In patients with extensive cutaneous lesions or with active involvement of the eye the treatment should be administered with great caution to avoid producing dangerous reactions

Measures for the Production of Reactions —Various additional measures have been used to produce controllable non specific febrile reactions which may stimulate the reparative processes These include the inoculation of foreign proteids such as milk or bacterial vaccines exposure to physical agents such as ultraviolet light radiant heat or hot baths and the use of iodides or other drugs Such procedures should be used cautiously and preferably by those trained in the treatment of leprosy

The control of Lepra Reaction —The following methods were outlined by the Leonard Wood Memorial Conference (1931) for the control of lepra reactions

(a) The patient should be put at rest and if there is no contra

McCoy in 1935 commented thoughtfully on the treatment of leprosy as follows — in recent years we have seen several therapeutic agents tried and found wanting. Indeed at present there is a tendency to put less emphasis on the medicinal agents and more on modifications of diet and such general measures as are applicable in the treatment of tuberculosis



Fig 9 Result of Treatment (From Wade and Rodriguez 1927) No 23 Cutaneous leprosy with advanced nodular lesions No 24 Showing marked improvement after one year of treatment (iodized ethyl esters)

Prophylaxis

The inadequate nature of our knowledge of the epidemiology of leprosy makes it difficult to formulate an effective plan for its prevention. However if the generally accepted modern concepts are correct it appears that the most important factors to be considered are (1) the recognition of infected individuals and (2) the prevention of their contact with normal persons especially with children including their own infants. The infants of lepers should be separated from their parents immediately after birth.

The principles of the prophylaxis of leprosy as outlined in the first general reports of the Leprosy Commission Health Organization of the League of Nations (1931) can be summarized as follows

Results of Chaulmoogra Treatment

It is generally agreed that the Chaulmoogra oil preparations do not afford a specific cure for leprosy and certain leprologists have even questioned the advisability of their therapeutic use Others however are convinced that in cases which are not too advanced these preparations are of distinct value, in that they often cause a marked general improvement with obliteration of local lesions which may be rendered at least temporarily free of demonstrable acid fast bacilli (see Fig 9)

According to Wade and Rodriguez In a case improving under treatment it will be found that after a variable number of injections depending chiefly on the advancement of the disease and the bodily vigor and probably specific resistance of the patient the lesions become less prominent and their coppery color changes to dark brown They gradually subside until the skin may appear practically normal However with long standing infiltrations and particularly old nodules a residue of thickened and reddish skin may remain for a long time On close examination the flushed appearance will be found to be due to distended capillary vessels Smears from such skin are bacteriologically negative

The anesthesia improves more gradually than the cutaneous lesions It may disappear completely if the process in the nerves is recent but when the nerve fibers have been completely destroyed and the trunks changed to fibrous tissue the anesthesia and whether or not from the same cause the trophic changes will remain permanently even though the patient may become entirely free from bacillus discharging lesions

The reports vary as to the proportion of cases which improve or are arrested by treatment According to Lara (1933) 47 lepers were released from Culion as apparently cured during the fifteen years from 1906 to 1922 while 2019 patients were paroled in the subsequent ten years (1922–1931) during which systematic Chaulmoogra treatment was used In the Philippines the relapse rates prior to parole have been about 43 per cent in the first six months 50 per cent in one year and 53 per cent in two years The relapse rates after parole have been reported as from 23 to 46 per cent (Philippine Leprosy Commission 1935) Denney in Carville La observed that with rigid parole requirements the relapses over a ten year period were only 3 per cent on the other hand Wayson in Hawaii found 51 per cent relapses within 3 5 to 5 years after parole Thus in spite of the striking clinical improvement seen in properly treated lepers there is little definite information concerning the proportion of permanent cures to be expected after treatment with the chaulmoogra preparations

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PROPHYLAXIS

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The principles of the prophylaxis of leprosy as outlined in the first general reports of the Leprosy Commission Health Organization of the League of Nations (1931) can be summarized as follows

1 Prophylaxis of leprosy is not a problem that admits of solution by the application of any one measure since the means of dealing with it obviously vary with geographical economic administrative financial and social conditions and with the incidence of the disease

2 There is no reliable system of prophylaxis without treatment and it is generally accepted that the earlier the treatment is instituted the better will be the results

3 Leprosy resembles tuberculosis in being in certain stages a contagious but curable disease curable at least in the sense that bacteriological examination becomes negative and other active signs disappear and remain absent permanently or for an undetermined period

4 The prophylaxis of leprosy may be achieved by a system of medical educative and legislative measures It should provide for the isolation and treatment of infectious lepers and particularly for the treatment of early cases in clinics and dispensaries also for the periodical examination of suspects Special measures should be adopted for dealing with the children of lepers and for patients who have recovered either after treatment or spontaneously

5 It is desirable that each country where leprosy exists to an important degree should have at least one center for the study of the disease with research laboratories and special courses for the medical profession and their assistants Where this is not practicable men should be sent to some foreign center for training

6 Arrangements should be made to include instruction in leprosy in the curriculum of all medical schools and colleges

7 It is necessary to educate the public in regard to leprosy by modern methods of popular teaching and propaganda

8 Isolation of infectious lepers is a necessary measure in a comprehensive campaign against leprosy but it cannot be regarded per se as the sole means of prophylaxis Its drawbacks can be mitigated by other measures applied concurrently Isolation should be applied only to cases that are considered infectious

9 Any form of treatment in order to give satisfactory results requires to be combined with suitable dietetic and general hygienic conditions

10 For special treatment oils of the chaulmoogra group and their esters and soaps are recommended

11 The system of prophylaxis must be animated by the spirit of preventive medicine and social hygiene

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